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UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

AMARIN PHARMA, INC., et al., Plaintiffs, v. HIKMA PHARMACEUTICALS USA, INC., et al., Defendants.	Case No. 2:16-cv-02525-MMD-NJK (Consolidated with Case No. 2:16-cv-02562-MMD-NJK) **DEFENDANTS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW**

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GLOSSARY OF ABBREVIATIONS

Amarin	Plaintiffs Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited
ANDA	abbreviated new drug application
Apo B	apolipoprotein B
Defendants	Defendants Hikma Pharmaceuticals USA Inc., Hikma Pharmaceuticals International Limited, Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.
DHA	docosahexaenoic acid
Dep. Tr.	Deposition transcript
DDX	Defendants' demonstrative exhibit
DX	Defendants' trial exhibit
EPA	eicosapentaenoic acid, which is also called icosapent, icosapent ethyl, ethyl icosapentate, or "EPA-E" (i.e., ethyl EPA)
FDA	U.S. Food and Drug Administration
FF	[Proposed] Findings of Fact
g	gram
IND	investigational new drug application
NDA	new drug application
LDL-C	low-density lipoprotein cholesterol
mg/dL	milligrams per deciliter
mmol/L	millimoles per liter
n-3	omega-3
PDR	Physicians' Desk Reference (a published compilation of drug labels)
Plaintiffs	Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited
PTO	U.S. Patent and Trademark Office
PDX	Plaintiffs' demonstrative exhibit
PX	Plaintiffs' trial exhibit
TG	triglycerides
Tr.	Trial transcript

I. INTRODUCTION

1. In October 2016, Plaintiffs Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited (collectively, "Plaintiffs" or "Amarin") filed suit against Defendants Hikma Pharmaceuticals USA Inc., Hikma Pharmaceuticals International Limited, Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "Defendants") under the Hatch-Waxman Act, 35 U.S.C. § 271(e). ECF No. 1. Defendants have filed abbreviated new drug applications ("ANDAs") with the FDA seeking approval for generic versions of Plaintiffs' Vascepa® capsules, which contain the active ingredient icosapent ethyl, also known as purified eicosapentaenoic acid ("EPA").

2. Plaintiffs allege under 35 U.S.C. § 271(b) that Defendants' marketing of their ANDA products would actively induce infringement of U.S. Patent Nos. 8,293,728 ("the '728 patent"), 8,318,715 ("the '715 patent"), 8,357,677 ("the '677 patent"), 8,367,652 ("the '652 patent"), 8,431,560 ("the '560 patent"), and 8,518,929 ("the '929 patent"). Defendants counterclaim for declaratory judgments that the asserted patents are not infringed and are invalid.

3. Collectively, Plaintiffs assert 10 claims of the patents-in-suit. These claims are generally directed to a method of reducing triglycerides in a patient with severe hypertriglyceridemia—i.e., a patient with triglycerides of at least 500 mg/dL—by administering about 4 g/day of purified EPA for at least 12 weeks. Three of the 10 asserted claims require that the patient being treated does not receive concurrent lipid altering therapy, e.g., a statin; the remaining seven asserted claims, however, are broad enough to include statin use. Nine of the 10 asserted claims require that the claimed method have specific effects on the patient's blood levels of triglycerides, low-density lipoprotein cholesterol ("LDL-C"), or apolipoprotein B ("Apo B").

4. For four independent reasons discussed in greater depth in the conclusions of law below, Defendants are entitled to judgment in their favor:

- First, Defendants will not induce infringement of any asserted claim because the labels for their proposed generic products do not instruct physicians to administer Defendants' products for at least 12 weeks, as required by all asserted claims.
- Second, all asserted claims are invalid under 35 U.S.C. § 103 because they were obvious, or at least obvious to try, in view of the prior art as of the date of the alleged invention (no earlier than March 25, 2008).

- Third, Defendants will not induce infringement of the three asserted claims that exclude concurrent lipid altering therapy, and the remaining seven claims that allow such therapy were at least obvious to try because co-administering a statin was reasonably expected to achieve all of the claimed effects.

- Fourth, Defendants will not induce infringement of the nine asserted claims that require specific effects on patients' lipids, and the remaining claim—which requires no lipid effects other than reducing triglycerides—was at least obvious to try.

II. FINDINGS OF FACT

A. Parties

5. Plaintiff Amarin Pharma, Inc. is a company organized and existing under the laws of Delaware with its principal place of business at 440 Route 22, Bridgewater, NJ 08807. Stipulated Facts, ECF No. 324 at ¶ 2.

6. Plaintiff Amarin Pharmaceuticals Ireland Limited is a company incorporated under the laws of Ireland with registered offices at 88 Harcourt Street, Dublin 2, Dublin, Ireland. Stipulated Facts, ECF No. 324 at ¶ 3.

7. Defendant Hikma Pharmaceuticals USA Inc. is a company organized and existing under the laws of Delaware with its principal place of business at 246 Industrial Way West, Eatontown, NJ 07724. Stipulated Facts, ECF No. 324 at ¶ 4.

8. Defendant Hikma Pharmaceuticals International Limited is a company incorporated under the laws of the United Kingdom with registered offices at 1 New Burlington Place, London, England W1S 2HR. Stipulated Facts, ECF No. 324 at ¶ 5.

9. Defendant Dr. Reddy's Laboratories, Inc. is a company organized and existing under the laws of New Jersey with its principal place of business at 107 College Road East, Princeton, NJ 08540. Stipulated Facts, ECF No. 324 at ¶ 6.

10. Defendant Dr. Reddy's Laboratories, Ltd. is an Indian public limited liability company organized and existing under the laws of India and having a principal place of business at 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Andhra Pradesh 500 034, India. Stipulated Facts, ECF No. 324 at ¶ 7.

B. Patents-in-suit

11. Amarin Pharmaceuticals Ireland Limited is the owner of the asserted patents. Stipulated Facts, ECF No. 324 at ¶ 8.

12. Each of the asserted patents is entitled "Methods Of Treating Hypertriglyceridemia." Stipulated Facts, ECF No. 324 at ¶ 9.

13. The U.S. Applications that ultimately issued as the asserted patents are continuations of U.S. Application No. 12/702,889, filed on February 9, 2010, which ultimately issued as U.S. Patent No. 8,293,727 ("the '727 Patent"). Stipulated Facts, ECF No. 324 at ¶ 10.

14. The asserted patents further claim priority to U.S. Provisional Application No. 61/151,291, filed on February 10, 2009, and U.S. Provisional Application No. 61/173,755, filed on April 29, 2009. Stipulated Facts, ECF No. 324 at ¶ 11.

15. The asserted patents share a common specification. DX 1500; DX 1502; DX 1504; DX 1506; DX 1514; DX 1516; *see also* Toth Tr. 1793:25-1794:2.

16. There is no data in the specification, clinical, animal, in vitro, or otherwise. DX 1500; DX 1502; DX 1504; DX 1506; DX 1514; DX 1516; Toth Tr. 1799:11-19. Instead, there are bare assertions and prospective protocols. DX 1500; DX 1502; DX 1504; DX 1506; DX 1514; DX 1516.

17. Mehar Manku, Ian Osterloh, Pierre Wicker, Rene Braeckman, and Paresh Soni are named as inventors of the asserted patents. Stipulated Facts, ECF No. 324 at ¶ 12.

1. The '728 Patent

18. The PTO issued the '728 Patent on October 23, 2012. Stipulated Facts, ECF No. 324 at ¶ 14.

19. Amarin Pharmaceuticals Ireland Limited filed U.S. Application No. 13/349,153, which ultimately issued as the '728 Patent, on January 12, 2012. Stipulated Facts, ECF No. 324 at ¶ 15.

20. U.S. Application No. 13/349,153 is a continuation of U.S. Application No. 12/702,889, filed on February 9, 2010, now the '727 Patent. Stipulated Facts, ECF No. 324 at ¶ 16.

2. The '715 Patent

21. The PTO issued the '715 Patent on November 27, 2012. Stipulated Facts, ECF No. 324 at ¶ 17.

22. The PTO issued a Certificate of Correction to the '715 Patent on August 11, 2015. Stipulated Facts, ECF No. 324 at ¶ 18.

23. The PTO issued a Certificate of Correction to the '715 Patent on May 21, 2019. Stipulated Facts, ECF No. 324 at ¶ 19.

24. Amarin Pharmaceuticals Ireland Limited filed U.S. Application No. 13/282,145, which ultimately issued as the '715 Patent, on October 26, 2011. Stipulated Facts, ECF No. 324 at ¶ 20.

25. U.S. Application No. 13/282,145 is a continuation of U.S. Application No. 12/702,889, filed on February 9, 2010, now the '727 Patent. Stipulated Facts, ECF No. 324 at ¶ 21.

3. The '677 Patent

26. The PTO issued the '677 Patent on January 22, 2013. Stipulated Facts, ECF No. 324 at ¶ 22.

27. Amarin Pharmaceuticals Ireland Limited filed U.S. Application No. 13/608,775, which ultimately issued as the '677 Patent, on September 10, 2012. Stipulated Facts, ECF No. 324 at ¶ 23.

28. U.S. Application No. 13/608,775 is a continuation of U.S. Application No. 13/349,153, filed on January 12, 2012, now the '728 Patent, which is a continuation of U.S. Application No. 12/702,889, filed on February 9, 2010, now the '727 Patent. Stipulated Facts, ECF No. 324 at ¶ 24.

4. The '652 Patent

29. The PTO issued the '652 Patent on February 5, 2013. Stipulated Facts, ECF No. 324 at ¶ 25.

30. Amarin Pharmaceuticals Ireland Limited filed U.S. Application No. 13/610,247, which ultimately issued as the '652 Patent, on September 11, 2012. Stipulated Facts, ECF No. 324 at ¶ 26.

31. U.S. Application No. 13/610,247 is a continuation of U.S. Application No. 13/349,153, filed on January 12, 2012, now the '728 Patent, which is a continuation of U.S. Application No. 12/702,889, filed on February 9, 2010, now the '727 Patent. Stipulated Facts, ECF No. 324 at ¶ 27.

5. The '560 Patent

32. The PTO issued the '560 Patent on April 30, 2013. Stipulated Facts, ECF No. 324 at ¶ 28.

33. Amarin Pharmaceuticals Ireland Limited filed U.S. Application No. 13/711,329, which ultimately issued as the '560 Patent, on December 11, 2012. Stipulated Facts, ECF No. 324 at ¶ 29.

34. U.S. Application No. 13/711,329 is a continuation of U.S. Application No. 13/623,450, filed on September 20, 2012, now the '920 Patent, which is a continuation of U.S. Application No. 13/349,153, filed on January 12, 2012, now the '728 Patent, which is a continuation of U.S. Application No. 12/702,889, filed on February 9, 2010, now the '727 Patent. Stipulated Facts, ECF No. 324 at ¶ 30.

6. The '929 Patent

35. The PTO issued the '929 Patent on August 27, 2013. Stipulated Facts, ECF No. 324 at ¶ 31.

36. Amarin Pharmaceuticals Ireland Limited filed U.S. Application No. 13/776,242, which ultimately issued as the '929 Patent, on February 25, 2013. Stipulated Facts, ECF No. 324 at ¶ 32.

37. U.S. Application No. 13/776,242 is a continuation of U.S. Application No. 13/711,329, filed on December 11, 2012, now the '560 Patent, which is a continuation of U.S. Application No. 13/623,450, filed on September 20, 2012, now the '920 Patent, which is a continuation of U.S. Application No. 13/349,153, filed on January 12, 2012, now the '728 Patent, which is a continuation of U.S. Application No. 12/702,889, filed on February 9, 2010, now the '727 Patent. Stipulated Facts, ECF No. 324 at ¶ 33.

7. Asserted Claims

38. Plaintiffs are asserting ten claims in this matter: claims 1 and 6 of the '728 patent; claim 14 of the '715 patent; claims 1 and 8 of the '677 patent; claim 1 of the '652 patent; claims 4 and 17 of the '560 patent; and claims 1 and 5 of the '929 patent.

39. No limitations in any asserted claim involve stroke, diabetes, or other cardiovascular risks. DX 1500; DX 1502; DX 1504; DX 1506; DX 1514; DX 1516. Plaintiffs have other patents that cover cardiovascular risk factors and benefits, but those patents are not asserted here and do not overlap with the asserted patents. DX2299.

40. None of the asserted claims require a combination therapy with statins, but seven claims allow such use (claims 1 and 8 of the '677 patent, claim 1 of the '652 patent, claims 4 and 17 of the '560 patent, and claims 1 and 5 of the '929 patent). DX 1500; DX 1502; DX 1504; DX 1506; DX 1514; DX 1516.

C. Witnesses at trial

1. Fact witnesses

41. Steve Ketchum is the only fact witness who testified live at trial. Dr. Ketchum is a Senior Vice-President, President of Research and Development, and the Chief Scientific Officer at Amarin. Dr. Ketchum has a large "financial interest" in the outcome of this case. *See* Ketchum Tr. 260:9-13. In fact, Dr. Ketchum owns roughly 545,000 shares of Amarin stock. Ketchum Tr. 258:8-19. This equates to roughly $10 million, depending on the share price on any given day. Ketchum Tr. 258:20-259:3. Dr. Ketchum owns more Amarin stock than any other employee except for the CEO. Ketchum Tr. 258:12-19.

42. None of the inventors testified live, and only two testified by deposition designation. Drs. Mehar Manku and Ian Osterloh are the only inventors who testified by deposition designation. Plaintiffs presented no testimony from the remaining three inventors: Pierre Wicker, Rene Braeckman, and Paresh Soni.

43. Other witnesses also testified through deposition designation. Plaintiffs introduced deposition testimony from the following fact witnesses: Jerald Andry, Jaya Ayyagari, Andrea Cady, and Howard Weintraub. Defendants introduced deposition testimony from Aaron Berg, Harold Bays,

Philip Lavin, and Michael Miller. Defendants also introduced testimony from Ian Osterloh and Mehar Manku for exhibit admissibility purposes only.

2. Plaintiffs' experts

44. Plaintiffs called expert witnesses Matthew Budoff (infringement), Carl Peck (infringement), Peter Toth (validity), and Sean Nicholson (commercial success).

45. Dr. Budoff testified as Plaintiffs' infringement expert. Dr. Budoff is a paid consultant and speaker for Amarin Pharmaceuticals unrelated to this litigation matter. Amarin has paid over $300,000 for Dr. Budoff's involvement in these types of activities. DX 2246; DX 3000-3005.

a. Dr. Budoff testified that a majority of this $300,000 went to his institution rather than to himself personally (Budoff Tr. 535:11-24), but that testimony is inconsistent with his deposition testimony, Amarin's submissions to FDA, and Amarin's submissions to the Centers for Medicare & Medicaid Services ("CMS"). During trial, Dr. Budoff was impeached with his deposition testimony where he explained that he had *personally* received over $300,000 dollars from Amarin unrelated to this case. Budoff Tr. 535:18-19. On multiple occasions, Amarin has been legally required to report how much money it has paid to Dr. Budoff personally. Dr. Budoff's deposition testimony—not his trial testimony—is consistent with what Amarin has reported to multiple agencies.

b. First, Amarin reported to FDA that it paid Dr. Budoff over $1 million from 2012 to 2019. DX 2246 at 7.[1] Of this total amount, $900,000 was paid out as a research grant, which went to Dr. Budoff's institution rather than him personally, for a study where Dr. Budoff is the principal investigator. *Id.* The other roughly $350,000, however, was paid to Dr. Budoff for consulting, honoraria, education, and other services such as speaker training and advisory board involvement. *Id.*

[1] For clarity and consistency, the pin cites throughout this document refer to the DX-stamped page numbers rather than the original document page numbers.

c. Second, Amarin's report to FDA is consistent with the figures that Amarin reported to CMS. "The law requires CMS to collect and display information reported by" drug manufacturers "about the payments and other transfers of value [that the organization] [has] made to physicians." DX 3017 (CMS Website) at 1. After the information is submitted by the drug company, there is a period where the physician is provided an opportunity to review and dispute the data. *Id.* Once the physician has had the opportunity to review and dispute the data—and the data has been corrected where necessary—the data is displayed on the CMS public website. *Id.* "Civil monetary penalties (CMPs) of up to $1,000,000 may be imposed on [an] organization if it fails to report information in a timely, accurate, or complete manner." DX 3018 (CMS Website) at 1. "CMS requires that [an] organization keep all records related to payments or other transfers of value for at least five years from the date that the payment or other transfers of value are posted." In other words, Amarin Pharmaceuticals is required to keep all records pertaining to physician compensation for at least five years.

d. Based on the data reported by Amarin to CMS, Dr. Budoff was paid over $310,000 serving as a faculty or as a speaker, consulting, honoraria, and education from 2013 to 2018. DX3000-3005. By regulation, drug manufacturers are required to report if a "payment or transfer of value was provided to a third party at the request of or designated on behalf of a covered recipient." 42 C.F.R. § 403.912(c)(10). No third-party institute is listed for any of the payments that were paid to Dr. Budoff. Instead, according to the CMS data, each payment from Amarin was provided to Dr. Budoff personally or to his personal company, Matthew Budoff Inc. DX3000-3005.

46. Dr. Toth testified as Plaintiffs' validity expert. Like Dr. Budoff, Dr. Toth is also a paid consultant and speaker for Amarin Pharmaceuticals unrelated to this litigation. Dr. Toth testified, while being impeached, that Amarin Pharmaceuticals has paid him at least $67,000 over the

last eight years. The CMS database shows that Dr. Toth has been paid $139,770.22 by Amarin over the last eight years, not including 2019. DX 3006. As discussed above, CMS provides several safeguards to ensure the database is accurate.

47. Dr. Peck testified as Plaintiffs' FDA infringement expert. In contrast to Drs. Budoff and Toth, Dr. Peck has never "worked for Amarin in any capacity prior to this case," and thus is an independent expert. Peck Tr. 1313:19-21.

48. Dr. Nicholson testified as Plaintiffs' commercial success expert.

3. Defendants' experts

49. Defendants called expert witnesses Jonathan Sheinberg (non-infringement), Jay Heinecke (invalidity), Edward Fisher (invalidity), and Ivan Hofmann (rebutting commercial success).

50. Dr. Sheinberg, a board-certified cardiologist, testified as Defendants' non-infringement expert. Apart from this litigation, Dr. Sheinberg has no affiliation with Defendants. Sheinberg Tr. 558:10-12. Thus, he is an independent expert.

a. Dr. Sheinberg earned his M.D. degree at Georgetown University School of Medicine. DX 2225; Sheinberg Tr. 559:21-560:1. After he received his medical degree, he "entered active duty with the United States Air Force and did [his] internship at Georgetown and Fairfax Hospital and [his] residency at Keesler Air Force Base in internal medicine." Sheinberg Tr. 559:23-560:5; *see also* DX 2225 (Sheinberg CV). Dr. Sheinberg completed his fellowship in cardiovascular disease (F.A.C.C.) at Wilford Hall Medical Center at Lackland Air Force Base. DX 2225 (Sheinberg CV); Sheinberg Tr. 560:6-9.

b. Dr. Sheinberg is currently employed at Baylor Scott & White Cardiology as a senior staff cardiologist. DX 2225 (Sheinberg CV); Sheinberg Tr. 557:24-558:6. Dr. Sheinberg treats patients with elevated triglycerides "every day" and sees "roughly 100 [cardiology] patients . . . per week, which averages [to] about 400 or so, plus or minus, per month." Sheinberg Tr. 560:18-24. More specifically, Dr. Sheinberg treats patients with severe hypertriglyceridemia

"on the order of approximately 20 to 30 per month." *Id.* at 560:25-561:4 (Sheinberg).

51. Dr. Heinecke, an endocrinologist and expert in lipoprotein metabolism and lipid disorders, testified as one of Defendants' invalidity experts. Apart from this litigation, Dr. Heinecke has no affiliation with Defendants. Heinecke Tr. 710:20-22. Thus, he is an independent expert.

a. Dr. Heinecke earned his M.D. degree at Washington University School of Medicine in St. Louis. DX 2222 (Heinecke CV); *see also* Heinecke Tr. 711:16-22. He completed his "training in internal medicine and a post-doctoral fellowship at the University of Washington." Heinecke Tr. 711:16-22; *see also* DX 2222 (Heinecke CV). He completed his post-doctoral fellowship "in the Division of Metabolism, Endocrinology, and Nutrition with a special emphasis on disorders of lipid metabolism." Heinecke Tr. 712:1-5; *see also* DX 2222 (Heinecke CV).

b. Dr. Heinecke has taught several medical education courses on hyperlipidemia and has treated patients with lipid disorders, including patients with severe hypertriglyceridemia. Heinecke Tr. 712:11-20, 712:21-713:8; *see also* DX 2222 (Heinecke CV). Dr. Heinecke's area of expertise is "[l]ipoprotein metabolism and the pathogenesis of atherosclerosis, otherwise known as hardening of the arteries." Heinecke Tr. 710:23-25.

52. Dr. Fisher, a biochemist and expert in cardiovascular medicine, also testified as one of Defendants' invalidity experts. Defendants called Dr. Fisher, in part, to rebut anticipated testimony from two of Plaintiffs' experts (Drs. Mason and Ismail), but Plaintiffs opted not to call either of these witnesses to testify at trial. Dr. Fisher has no relationship with Defendants aside from work on this litigation matter. Fisher Tr. 942:4-7. Thus, he is also an independent expert.

a. Dr. Fisher received his M.D. degree from NYU School of Medicine and completed his residency at Duke. DX 2295; Fisher Tr. 8-15. After his residency, Dr. Fisher attended the University of North Carolina in Chapel Hill where he studied epidemiology and received a Master's of Public Health. DX

2295; Fisher Tr. 8-15. After that, Dr. Fisher went to MIT where he received a Ph.D in the area of lipoprotein metabolism. DX 2295 (Fisher CV); Fisher Tr. 16-17. Dr. Fisher has an ongoing relationship in cardiovascular medicine at the University of Oxford where he was appointed as an Eastman Professor in the cardiovascular medicine department. Fisher Tr. 928:8-17; *see also* DX 2295 (Fisher CV).

b. During his career, Dr. Fisher "started a family-based clinic for the treatment of lipid disorders." Fisher Tr. 926:12-13; *see also* DX 2295 (Fisher CV). Dr. Fisher was also the founding director of the Center for Prevention of Cardiovascular Disease at NYU. Fisher Tr. 929:3-6; *see also* DX 2295 (Fisher CV).

53. Mr. Hofmann, an economist, testified as Defendants' commercial success expert. Like Defendants' other experts, Mr. Hofmann is an independent expert.

a. Mr. Hofmann graduated "magna cum laude from the University of Notre Dame with majors in both economics and accounting." Hofmann Tr. 1219:4-5; DX 2223 (Hofmann CV). Mr. Hofmann is currently the Vice-President and Managing Director at Gleason. DX 2223 (Hofmann CV). Gleason "is an economic finance and accounting consulting firm" where Mr. Hofmann is "the leader of the intellectual property practice." Hofmann Tr. 1218:24-1219:2; DX 2223 (Hofmann CV).

b. Mr. Hofmann has previously worked with and studied products that are used to reduce triglyceride levels in adult patients with severe hypertriglyceridemia from an economic perspective. Hofmann Tr. 1220:2-8.

D. Vascepa and Defendants' ANDA products

54. Amarin Pharmaceuticals Ireland Limited is the holder of New Drug Application ("NDA") No. 202057 for a highly purified preparation of EPA ethyl ester sold under the brand name Vascepa®. DX 2248 (Vascepa Label) at 1. Amarin received FDA approval for 1 g capsules of Vascepa® on July 26, 2012. Stipulated Facts, ECF No. 324 at ¶ 180.

55. Pursuant to 21 U.S.C. § 355(b)(1), the asserted patents are listed in the "Orange Book"—published by FDA and formally known as *Approved Drug Products with Therapeutic Equivalence Evaluations*—in connection with NDA No. 202057. Stipulated Facts, ECF No. 324 at ¶ 13.

1. Vascepa indications

56. Vascepa has two FDA-approved indications—referred to at trial as the "MARINE Indication" and the "REDUCE-IT" Indication." Ketchum Tr. 64:5-65:10; DX 2248 (Vascepa Label).

57. The MARINE Indication "was first approved in July of 2012." Ketchum Tr. 65:11-12. This indication is "based on" "the MARINE trial" and states that Vascepa is to be used "[a]s an adjunct to diet to reduce TG levels in adult patients with severe (greater than or equal to 500 mg/dL) hypertriglyceridemia." *Id.* at 64:24-65:10 (Ketchum); DX 2248 (Vascepa Label).

58. The REDUCE-IT indication was later approved in 2019 and is "based on the results of" "the REDUCE-IT large long-term cardiovascular outcomes trial." Ketchum Tr. 64:7-23. This indication covers the use of Vascepa to reduce the risk of "myocardial infraction, stroke, coronary revascularization, and unstable angina requiring hospitalization" in patients that had "elevated triglyceride (TG) levels (≥ 150 mg/dL)," and either an "established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." DX 2248 (Vascepa Label).

2. Regulatory exclusivities

59. FDA approved Vascepa in 2012 for the severe-hypertriglyceridemia indication based on the MARINE clinical study. The reward for a successful study that leads to an approved indication is not patent protection—it is a period of regulatory exclusivity. *See* 21 U.S.C. § 355(j)(5)(F)(iii). "[R]egulatory exclusivity means that FDA [will not] approve any generic product for some particular period" of time. Ketchum Tr. 167:9-14. The purpose of a regulatory exclusivity "is to acknowledge that the sponsor, in arriving at [an] expanded indication[,] has exerted a certain amount of time, energy, and financial wherewithal to get to that" indication. *Id.* (Ketchum).

60. FDA awards three years of exclusivity when an application contains a new clinical trial, and five years when an application contains a new chemical entity ("NCE"). 21 C.F.R. § 314.108. FDA regulations define a "new chemical entity" as "[a] drug that contains no active

moiety that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 C.F.R. § 314.108(a).

61. When it filed its NDA, Amarin sought five years of NCE exclusivity on the ground that, although it did not invent purified EPA, it was the first party to obtain FDA approval for a purified EPA product for sale in the United States. FDA initially disagreed because there was another fish oil drug product already approved to treat triglyceride levels in people with severe hypertriglyceridemia: Lovaza. After FDA denied the NCE exclusivity, Amarin challenged the agency and ultimately won in court. *Amarin Pharms. Ireland Ltd. v. FDA*, No. 14-cv-00324 (RDM) (D.D.C. May 28, 2015). Following the court's opinion, the FDA granted Amarin's NCE exclusivity request. DX 2254 (FDA Vascepa Exclusivity Determination Letter). Thus, Amarin received "five years of new chemical entity exclusivity for the MARINE indication." Ketchum Tr. 169:10-12.

62. Because the FDA ultimately granted the NCE exclusivity, the FDA could not approve any other drug containing purified EPA for five years, and could not even accept an application to market generic Vascepa for four years. 21 U.S.C. § 355(j)(5)(F)(ii).

63. Amarin publically announced on May 31, 2016 that the "NCE exclusivity for Vascepa runs from its date of FDA approval on July 26, 2012 and extends until July 26, 2017. The statutory 30-month stay [under the Hatch-Waxman amendments] triggered by patent litigation following generic application submissions permitted on July 26, 2016 would expire on January 26, 2020, seven-and-a-half years from FDA approval." DX 2255 (Amarin News Release re: Market Exclusivity Determination) at 1. Therefore, "the total amount of exclusivity plus the 30-month stay totals seven-and-a-half years," which means that "Amarin received seven-and-a-half years of regulatory exclusivity" and "was free from generic competition for that entire period." Ketchum Tr. 170:20-171:1; DX 2255, Amarin News Release re Market Exclusivity Determination.

64. Based on MARINE, FDA approved Vascepa for the same indication as Lovaza—"as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." DX 2248 (Vascepa Label) at 1-2.

65. In 2014, Amarin sought approval of a second indication that included co-administration therapy with statins in adult patients with mixed dyslipidemia or coronary heart

disease ("CHD"), or a CHD risk equivalent, to reduce TGs, non-HDL-C, Apo B, LDL-C, TC, and VLDL-C. DX 1836 (Amarin Formal Dispute Resolution Request ("FDRR")). In support, Amarin cited the prior-art "JELIS" study on Epadel, which Amarin characterized as "a very large, well-designed study" whose "results should not be dismissed lightly." *Id.* at 71. This indication, if approved, would have included patients at high risk for CHD, like diabetic patients, with triglyceride levels below 500 mg/dL. *Id.* Citing the rigorous standards for drug approval, however, FDA rejected Amarin's proposed indication and required Amarin to complete the REDUCE-IT study on Vascepa. As a result, Vascepa is not FDA-approved to reduce Apo B. After completing REDUCE-IT, Amarin again sought approval for a new indication.

66. The investigators who conducted REDUCE-IT acknowledged that the previous success of JELIS "led to the design of . . . REDUCE-IT." DX 1641 (Bhatt et al., *Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia*, N. Eng. J. Med. 380:1, 11-22 (2019) 1677-1678 ("Bhatt")). As JELIS predicted, REDUCE-IT showed a reduction in cardiovascular risk, this time by 25%. *Id*. at 9. Based on that result, in December 2019, FDA approved a new indication for Vascepa "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dl) and established cardiovascular disease, or diabetes mellitus and at least two more cardiovascular risk factors." DX 2248 (Vascepa Label). The new indication, and all information in the Vascepa labeling relating to it, is separate from Vascepa's original indication for severe hypertriglyceridemia, which remains materially unchanged. *See id*.

67. Because of REDUCE-IT, "Amarin will be entitled to additional exclusivity on the basis of having undertaken work . . . deemed to be essential for reviewing and approving an expanded indication for an additional use." Ketchum Tr. 167:3-8. More specifically, "Amarin will be entitled to another three years of exclusivity related to the REDUCE-IT indication," meaning that "there [will not] be generic competition in terms of generic products that [have] the REDUCE-IT indication in their label for at least three years regardless of patents." *Id.* at 173:11-19 (Ketchum).

3. Defendants' ANDA products

68. In 2016, after Vascepa's initial exclusivity against generic competition expired, Defendants filed ANDAs seeking FDA approval to market generic versions of Vascepa. As required by law, Defendants' ANDAs adopted the "same" labeling as Vascepa, which at the time was only approved for severe hypertriglyceridemia. 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(4)(G). Because Vascepa has two indications, however, the law "permits [Defendants] to file ANDAs directed to a subset of FDA-approved indications and even provides a mechanism for [Defendants] to affirmatively carve out" the new indication from their labels.[2] *See* DX 2256 (Hikma Label); DX 2266 (DRL Label).

a. Hikma's ANDA product

69. On or about September 21, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc., through Roxane Laboratories, Inc. (incorporated in Nevada), submitted to FDA an ANDA (ANDA No. 209457) with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of Vascepa (icosapent ethyl) 1 g capsules as Icosapent Ethyl Capsules, 1 gram ("Hikma's ANDA Product"). Stipulated Facts, ECF No. 324 at ¶ 183.

70. On or about July 26, 2016, Hikma Pharmaceuticals PLC and Roxane Labs., Inc., through Roxane Labs., Inc., submitted to FDA a proposed labeling for Hikma's ANDA product bearing revision date of "07/2016." Stipulated Facts, ECF No. 324 at ¶ 184.

71. Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated September 21, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. notified Amarin that they had submitted to FDA ANDA No. 209457, with paragraph IV certifications for the asserted patents.

72. On or about December 8, 2016, Roxane Laboratories, Inc. transferred ANDA No. 209457 to West-Ward Pharmaceuticals International Limited. Stipulated Facts, ECF No. 324 at ¶ 186.

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[2] *AstraZeneca Pharms. LP v. Apotex Corp*, 669 F.3d 1370, 1381 (Fed. Cir. 2012); *see also* 21 U.S.C. § 355(j)(2)(A)(viii); *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 406 (2012) (noting that Hatch-Waxman "allows the generic company to place its drug on the market . . . for a subset of approved uses").

73. On or about December 8, 2016, West-Ward Pharmaceuticals International Limited appointed West-Ward Pharmaceuticals Corp. as its agent for purposes of communication with FDA regarding ANDA No. 209457. Stipulated Facts, ECF No. 324 at ¶ 187.

74. West-Ward Pharmaceuticals International Limited has changed its name to Hikma Pharmaceuticals International Limited. Stipulated Facts, ECF No. 324 at ¶ 189.

75. West-Ward Pharmaceuticals Corp. has changed its name to Hikma Pharmaceuticals USA Inc. Stipulated Facts, ECF No. 324 at ¶ 190.

76. On or about July 8, 2019, Hikma Pharmaceuticals International Limited transferred ANDA No. 209457 to Hikma Pharmaceuticals USA Inc. Hikma Pharmaceuticals USA Inc. is now the owner of ANDA No. 209457. Stipulated Facts, ECF No. 324 at ¶ 191.

77. On or about December 30, 2019, Hikma Pharmaceuticals USA Inc. submitted to FDA a revised proposed labeling for Hikma's ANDA Product bearing revision date of "12/2019." DX 2256 (Hikma Label). Stipulated Facts, ECF No. 324 at ¶ 192.

b. DRL's ANDA product

78. On or about September 22, 2016, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA an ANDA (ANDA No. 209499) with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of Vascepa (icosapent ethyl) 1 g capsules as Icosapent Ethyl Capsules, 1 gram ("DRL's ANDA Product"). Stipulated Facts, ECF No. 324 at ¶ 193.

79. On or about July 26, 2016, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a proposed labeling for DRL's ANDA product bearing revision date of "06/2016." Stipulated Facts, ECF No. 324 at ¶ 194.

80. Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated September 22, 2016, DRL notified Amarin that it had submitted to FDA ANDA No. 209499, with paragraph IV certifications for the asserted patents. Stipulated Facts, ECF No. 324 at ¶ 195.

81. On or about January 4, 2017, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a revised proposed labeling for DRL's ANDA Product bearing revision date of "01/2017." Stipulated Facts, ECF No. 324 at ¶ 196.

82. On or about July 11, 2018, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a supplement to ANDA No. 209499 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for 500 mg icosapent ethyl capsules purportedly bioequivalent to Vascepa. Stipulated Facts, ECF No. 324 at ¶ 197.

83. Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated July 11, 2018, DRL notified Amarin that it had submitted to FDA a supplement to ANDA No. 20499, with paragraph IV certifications for the '728, '715, '677, '652, and '929 patents. Stipulated Facts, ECF No. 324 at ¶ 198.

84. On or about July 23, 2018, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a revised proposed labeling for DRL's ANDA product bearing revision date of "04/2018." Stipulated Facts, ECF No. 324 at ¶ 199.

85. On or about January 10, 2020, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a revised proposed labeling for DRL's ANDA product bearing revision date of "01/2020." DX 2266 (DRL Label).

E. Facts relevant to noninfringement

1. Severe hypertriglyceridemia and its treatment

a. Severe hypertriglyceridemia is not necessarily a chronic condition, and can be an acute condition.

86. "Hypertriglyceridemia" is not a discrete disease. Sheinberg Tr. 568:3-6. Rather, the term refers to having elevated triglycerides, which are the most abundant type of fat in the blood. The clinical guidelines that both sides rely on in this case, called "ATP III," define "normal triglycerides" as less than 150 mg/dL, with levels above that considered elevated to various degrees. DX 1526 (National Institutes of Health, National Heart, Lung, and Blood Institute, "Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), Executive Summary," May 2001 ("ATP-III Executive Summary")) at 27; *see also* Budoff Tr. 329:4-17. These numbers are referring to the "concentrations of triglycerides in the blood, and [] are always taken in the fasting state." Budoff Tr. 329:4-17.

87. Severe hypertriglyceridemia "has a well-known meaning to doctors who treat the condition." *Id.* at 454:6-8 (Budoff). It "means that a patient has had triglycerides levels greater than or equal to 500 milligrams per deciliter." Ketchum Tr. 52:24-3; *see also* Budoff Tr. 454:9-12. In other words, "as long as the patients have triglyceride [("TG")] levels above 500, regardless of why, they have severe hypertriglyceridemia." Budoff Tr. 455:8-11. This definition is consistent with the ATP-III guidelines as well as the Vascepa indication. DX 1526 (ATP-III Executive Summary) at 27; DX 2248 (Vascepa Label).

88. For most patients with elevated triglycerides, "the primary aim of therapy is to achieve the target goal for LDL cholesterol." DX 1526 (ATP-III Executive Summary) at 27. This is because research has long shown that "elevated LDL cholesterol is a major cause of CHD"—i.e., coronary heart disease. *Id*. at 11.

89. The primary aim of therapy is different in patients with severe hypertriglyceridemia because they have an elevated risk of acute pancreatitis. In patients with severe hypertriglyceridemia, the primary "aim of therapy is to prevent acute pancreatitis through triglyceride lowering." Budoff Tr. 457:11-15; *see also* DX 1526 (ATP-III Executive Summary) at 19. This is the "primary treatment aim [in patients with severe hypertriglyceridemia] regardless of why the patient has triglycerides above 500." Budoff Tr. 457:16-18.

90. In other words, severe hypertriglyceridemia is used as a marker for the risk of pancreatitis. "[D]octors know that when patients have triglycerides above 500, the goal is to prevent an acute pancreatitis attack." *Id.* at 455:15-18 (Budoff). This is because "pancreatitis can be a life-threatening condition." *Id.* at 473:18-20 (Budoff); *see also* Sheinberg Tr. 568:10-16.

91. Severe hypertriglyceridemia is "not always a chronic condition." Budoff Tr. 449:1-3. Indeed, "severe hypertriglyceridemia can be an acute phenomenon." *Id.* at 450:12-15 (Budoff).

92. At trial, Plaintiffs cited a checklist in the FDA's Medical Review for Vascepa as evidence that severe hypertriglyceridemia can be considered a chronic condition. Ketchum Tr. 108:5-14; DX 2116 (FDA Medical Review) at 142. For "chronically administered drugs," the checklist requires that "an adequate number of patients" have "been exposed" to the drug "at the dose (or dose range) believed to be efficacious." DX 2116 (FDA Medical Review) at 142. The checklist, however,

does not state or imply that Vascepa must be administered chronically to all patients. *Id.* Rather, because Vascepa *can be* used chronically in certain patients (e.g., those patients who have severe hypertriglyceridemia due solely to genetic factors), FDA requires information showing that the drug is safe for long-term use. No expert witness addressed this FDA checklist at trial, much less testified that it provides any evidence that FDA considers severe hypertriglyceridemia to be a chronic condition in all patients (such as, for example, HIV, or Multiple Sclerosis).

93. In fact, the evidence at trial suggested that FDA does not consider severe hypertriglyceridemia to be a chronic condition in all patients. As Dr. Budoff admitted, "there was a proposal to FDA from Amarin to characterize the Vascepa patient population as requiring chronic care, but FDA rejected" the proposal. Budoff Tr. 448:8-11; *compare* DX 2248 (Vascepa Label) *with* DX 2247 (Vascepa Proposed Label).

94. More specifically, Amarin attempted to add the following statement into section 6.2: "Because these reactions are reported voluntarily *from a chronic care population* of uncertain size and uncertain use of concomitant medications, it is generally not possible to reliably estimate the frequency of such reactions or establish causal relationship to drug exposure." DX 2247 (Vascepa Proposed Label) at 4 (emphasis added). In the FDA approved label, this statement instead reads: "Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a casual relationship to drug exposure." DX 2248 (Vascepa Label) at 4. Thus, the only reference to the indicated population as requiring "chronic care" in the Vascepa label (and, by extension, Defendants' labels) was removed by FDA. FDA removed the "chronic care population" phrasing without any comment. DX 2249 (sNDA Labeling Correspondence) at 7.

95. "[S]evere hypertriglyceridemia has various causes," and "the diagnosis of severe hypertriglyceridemia does not turn on the cause." Budoff Tr. 455:2-7.

96. There are several "reversible causes" of severe hypertriglyceridemia, including "diabetes out of control, binge drinking, [and] hypothyroidism." *Id.* at 449:9-13 (Budoff). All of these are "causes that can push people up into the severe hypertriglyceridemic range that would not be considered a chronic condition." *Id.* at 449:9-13 (Budoff).

97. As shown on Amarin's website for Vascepa, reversible causes of severe hypertriglyceridemia include (1) poor "diet," "especially alcohol and processed carbohydrates;" (2) "lack of exercise;" (3) "medical conditions;" and (4) "specific drugs," "including estrogen tablets." DX 1982.

98. While genetics may play a role in some patients with severe hypertriglyceridemia, Dr. Budoff agreed that "pure genetic disorders" are "rare," and that "the cause of severe hypertriglyceridemia in most patients is not solely genetics." Budoff Tr. 463:1-5, 468:5-11; *see also id*. at 468:15-19 (Budoff). "[I]t's less rare for patients to have a genetic predisposition to high triglycerides, and there are other factors that cause them to go above 500." *Id.* at 463:7-11 (Budoff). Thus, in these more common scenarios, severe hypertriglyceridemia is caused by a combination of (1) genetic predispositions (as opposed to disorders) to TG levels that are elevated, but not severe; and (2) lifestyle factors. In other words, the "patients may be genetically predisposed to high triglycerides," but "poor lifestyle choices contribute to the condition." *Id.* at 485:25-486:7 (Budoff).

99. Amarin's validity contentions in this case admit that "both diet and exercise level could have significant impacts on TG levels. Heavy consumption of carbohydrates, certain kinds of fats, and/or alcohol was understood to lead to increased TG levels." DX 1953 (Plaintiffs' Preliminary Validity Contentions) at 29. Amarin's contentions further admit that "regular exercise could offset the TG effects of some dietary factors and decrease TG levels. Accordingly, lack of regular exercise and/or sedentary lifestyle were known to correlate with higher TG levels." *Id*.

100. Similarly, Amarin's claim construction expert, Dr. Miller, authored a clinical guidance paper that lists "[p]regnancy (especially in the third trimester)," "[d]rugs (medications)," and "[a]lcohol excess" as causes of severe hypertriglyceridemia. DX 1632 (Miller et al., *Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association*, 123:2292-2333 (2011) ("Miller 2011")) at 11. Of course, "pregnancy in the third trimester is not a chronic condition." Budoff Tr. 482:8-10. Likewise, several of the drugs listed in Miller 2011 that cause severe hypertriglyceridemia "can be taken for less than 12 weeks," such as "steroids . . . [and] interferon." *Id.* at 482:11-21 (Budoff).

b. Severe hypertriglyceridemia does not require long-term drug treatment for at least 12 weeks.

101. Regardless of the cause of a particular patient's severe hypertriglyceridemia, severe hypertriglyceridemia does not necessarily require any drug treatment, much less at least 12 weeks of drug treatment. Thus, "Vascepa is suitable to reduce triglyceride levels in patients suffering from severe hypertriglyceridemia in less tha[n] 12 weeks." Budoff Tr. 498:5-8; *see also* ECF No. 278 at 11-13.

102. As an initial matter, clinical guidance that both sides rely on teaches that "[t]he cornerstone for the treatment of hypertriglyceridemia is lifestyle intervention with diet and exercise." DX 1957 (Karalis, *A Review of Clinical Practice Guidelines for Management of Hypertriglyceridemia*, 34 ADV. THER. 300-232 (2017) ("Karalis 2017")) at 6.

103. Amarin's own researchers concluded that lipid-lowering "diets are remarkable in how quickly they lower serum TGs." PX 833 (Friedewald et al., *The Editor's Roundtable: Hypertriglyceridemia*, 112 Am. J. Cardiology 1133 (2013) ("Friedewald 2013")) at 4. As they explained, "a change in diet can cause a huge change in TGs, and this is independent of the effect of diet on adiposity." *Id.*; *see also* Sheinberg Tr. 582:4-7. Likewise, "even modest increases in physical activity can have significant effects in reducing TGs." PX 833 (Friedewald 2013) at 5.

104. Lifestyle intervention is not limited to weight loss. Instead, "multiple interventions can yield additive triglyceride-lowering effects that result in significant reductions in triglyceride levels." DX 1632 (Miller 2011) at 20; Sheinberg Tr. 704:6-8. Some of these other lifestyle modifications include: "[d]iscontinuation of sugared beverages, discontinuation of alcohol, discontinuation of tobacco products, and the development and successful engagement into an exercise regimen consisting mostly [of] aerobic exercise, but also some anaerobic exercise to increase lean muscle mass." Sheinberg Tr. 704:11-15.

105. Amarin's claim construction expert, Dr. Miller, also confirmed in his clinical guidance paper that "optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%." DX 1632 (Miller 2011) at 24. Dr. Budoff agreed with this statement. Budoff Tr. 484:16-485:7. Dr. Miller's paper states that, "[a] weight loss of 5% to

10% results in a 20% decrease in triglycerides," and a "[m]editerranean-style diet . . . is more commonly associated with an approximately 10% to 15% lowering of triglycerides and a reduced prevalence of hypertriglyceridemia." DX1632 at 20, 22. Again, Dr. Budoff agreed. Budoff Tr. 483:21-484:8.

106. A "patient's triglyceride levels are fluid and change." Weintraub Dep. Tr. 48:17-21. "[I]n fact a patient's triglyceride levels can vary significantly based on lifestyle and medication changes." Budoff Tr. 483:17-20. For example, Dr. Budoff admitted that "weight loss of 5 to 10 percent results in a 20 percent decrease in triglycerides," and "[r]eductions of 50 percent or more in triglyceride levels may be attained through intensive therapeutic lifestyle change." *Id*. at 483:21-25, 484:21-2 (Budoff). In his "personal practice," Dr. Budoff generally "see[s] diet and exercise alone without any drugs decrease triglyceride levels by about 25 percent." *Id*. at 491:9-12 (Budoff). "[A]bout 20 percent of [his] patients with severe hypertriglyceridemia are able to reduce their triglyceride levels below 500 with diet and exercise alone," and "don't necessary need any drug therapy to get their levels below 500." *Id*. at 496:5-13 (Budoff).

107. However, even "if a patient engages in appropriate nutritional intake and physical activity for four to six weeks and still has triglycerides above 500, [that does not] necessarily mean that that patient has a chronic, long-term cause of severe hypertriglyceridemia." Sheinberg Tr. 638:15-20. This is because "[s]ometimes it takes longer than that" for lifestyle changes to effect a change in triglyceride levels. *Id.* at 638:4-8 (Sheinberg).

108. Given that lifestyle modifications can effectively reduce and maintain triglyceride levels, long-term drug therapy is often not necessary. Amarin's expert, Dr. Budoff, agrees that "a patient with severe hypertriglyceridemia does not necessarily require indefinite drug therapy." Budoff Tr. 489:19-22. "[M]any patients with severe hypertriglyceridemia don't require any drug therapy at all," because they can decrease and maintain triglyceride levels below 500 mg/dL with diet and exercise alone. *Id*. at 489:23-25 (Budoff); *see also id.* at 491:9-12 (Budoff). These patients could benefit from short-term icosapent therapy to decrease triglyceride levels immediately—before the diet and exercise regimen has the desired effect. Sheinberg Tr. 636:2-5; *see also id.* at 636:17-637:7 (Sheinberg).

109. Moreover, as Dr. Budoff conceded, "about 5 percent of [his] patients with severe hypertriglyceridemia take Vascepa for less than 12 weeks." Budoff Tr. 501:11-14. Thus, "physicians could follow the Vascepa labeling and treat severely hypertriglyceridemia patients with Vascepa 4 grams per day for fewer than 12 weeks and achieve an effect." *Id.* at 497:25-498:4 (Budoff); *see also* Sheinberg Tr. 630:8-10.

110. For "a patient who has [triglyceride levels] just barely above 500, let's say 510, and the patient can reduce their triglyceride level by 25 percent with diet and exercise eventually, . . . a doctor reasonably could prescribe icosapent for short term use to reduce the pancreatitis risk as soon as possible." Budoff Tr. 500:7-13. Once "triglyceride levels have been lowered to < 500 mg/dL," a physician's focus should again "turn to LDL lowering to reduce risk for CHD" rather than TG-lowering to reduce pancreatitis. DX 1526 (ATP-III Executive Summary) at 28.

111. "If the TG levels fall to a normal or borderline level with lifestyle changes . . . , consideration may be given to discontinuing the non-statin TG-lowering medication." DX 1957 (Karalis 2017) at 6. This is consistent with Dr. Budoff's practice where some of his "patients with severe hypertriglyceridemia stopped taking icosapent because they don't need to take the drug long-term to keep triglycerides below 500." Budoff Tr. 498:12-15.

112. In other words, once a patient's triglycerides have been reduced below 500 mg/dL with Vascepa (which takes significantly less than 12 weeks), those triglyceride reductions can often be maintained long-term with diet and exercise alone—i.e., the primary treatments for severe hypertriglyceridemia. Thus, for many (if not most) causes of severe hypertriglyceridemia, long-term drug therapy is often not required. A short course of drug treatment for less than 12 weeks, followed by maintenance therapy with diet and exercise alone, is sufficient for many, if not most, patients. Sheinberg Tr. 583:6-13. Thus, for various reasons, patients "frequently" stop taking Vascepa even if they still have pills left in their prescription. Sheinberg Tr. 705:11-13.

113. Doctors are also able to give "patients [Vascepa] samples which are provided by the manufacturer." Sheinberg Tr. at 705:14-17. These samples do not provide a 12-week supply of EPA. *Id.* at 705:25:706:2 (Sheinberg). Instead, the samples "contain a small pill bottle with two days worth

of samples," and patients are given "eight to 15 bottles," depending on availability. *Id.* at 705:19-24 (Sheinberg).

114. When physicians prescribe Vascepa for more than 12 weeks, it is often for reasons other than reducing or maintaining triglycerides below 500 mg/dL. *Id.* at 705:4-7 (Sheinberg). In other words, although physicians often choose to prescribe Vascepa for longer periods than 12 weeks, physicians do *not* typically do so because of the indicated use for treating severe hypertriglyceridemia. *Id.* at 591:9-592:11 (Sheinberg). Doctors may continue to prescribe Vascepa long term, even where it is not necessary to maintaining TG levels below 500, "because it might have additional benefits." Budoff Tr. 500:7-19.

115. Even before FDA approved the new Vascepa indication, the vast majority of Vascepa prescriptions—over 75%—have been for non-infringing uses of treating patients with triglycerides below 500 mg/dL. DDX 8.13; Hofmann Tr. 1252:23-1254:4; PDX 5-24; Nicholson Tr. 1497:8-25. Dr. Budoff testified that in his practice about 85% of uses are off-label. Budoff Tr. 508:20-509:4. That number is expected to increase significantly because of the addition of the REDUCE-IT indication—meaning just a small fraction of Vascepa prescriptions will implicate the patents-in-suit. Hofmann Tr. 1257:6-13.

116. There are several reasons why a physician might prescribe Vascepa (or Defendants' ANDA products) for at least 12 weeks other than to treat severe hypertriglyceridemia. For example, as discussed, Vascepa was recently approved to reduce cardiovascular risk in certain patients, and was previously prescribed off-label for the same purpose based on the REDUCE-IT study. DX 2248 (Vascepa Label); DX 1641 (Bhatt 2019) at 1. Unlike severe hypertriglyceridemia, which icosapent can treat within four weeks, REDUCE-IT suggests that it takes more than a year for daily icosapent use to reduce a patient's cardiovascular risk. *See* DX 1641 (Bhatt 2019) at 5, Fig. 1. However, using Vascepa or "[D]efendants' products should they come to market, solely to reduce cardiovascular risk, would be using icosapent off label." Budoff Tr. 460:17-21. "[D]efendants' products will not be indicated for [these] cardiovascular effects." *Id.* at 508:17-19 (Budoff).

117. Moreover, "icosapent is fairly well tolerated . . . so there's not too much of a downside if your patient is tolerating the medication, and they don't necessarily need it for severe

hypertriglyceridemia, to tell them to continue the medication because there may be cardiovascular benefits." *Id.* at 507:20-508:2 (Budoff). For example, Dr. Budoff "routinely, before and now after the new [REDUCE-IT] indication, [has] been prescribing Vascepa often to address triglyceride levels that are not above 500 but are still too high." *Id.* at 508:12-16 (Budoff).

118. The physician's choice of whether to discontinue icosapent use is often made before the patient has completed 12 weeks of drug treatment. For example, after prescribing icosapent, a physician may see her patient again after only two months or less. More specifically, physicians see patients again before 12 weeks of being on Vascepa "[v]ery frequently." Sheinberg Tr. 615:25-616:1. Even when a physician targets 12 weeks as the next office visit, scheduling conflicts may result in seeing the patient again after only about 10 or 11 weeks. And, patients may call their physicians ahead of the next office visit and ask whether they can discontinue the drug. *Id.* at 615:11-19 (Sheinberg). For example, patients may want to discontinue the drug because the pill is large and hard to swallow, because of side effects such as upset stomach, or due to costs. *Id.* at 616:5-25 (Sheinberg). Patients can thus seek and obtain physician approval to discontinue the drug before 12 weeks of drug treatment, which is consistent with the labeling for Defendants' ANDA products.

2. MARINE trial

119. FDA's approval of Vascepa® was based on the MARINE Study, which was a twelve-week, Phase 3, international, double-blind, randomized, placebo (mineral oil)-controlled trial. DX 1741 (Bays, et al., *Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients with Very High Triglyceride Levels (from the Multi-center, Placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] Trial)*, Am. J. Cardiol. 108(5): 682-90 (2011) ("Bays 2011")) at 1.

120. The MARINE study was initiated on December 14, 2009. DX 1694 (*Clinical Study Report: A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels ≥500 mg/dL & ≤2000 mg/DL: The AMR101 MARINE Study* (2011) ("MARINE Study Report")) at 1. The treatment period for the MARINE study finished in October

2010 and the results were unblinded (i.e. available to Amarin internally) in November 2010. *Id.* at 3. The MARINE study results were published in June 2011. DX 1741 (Bays 2011).

121. "The primary study endpoint [in the MARINE Study] was the placebo-corrected median percentage of change in TG [levels] from baseline to study end (week 12)." *Id.* at 2. The "additional efficacy end-points" also included "total cholesterol, [and] LDL cholesterol." *Id.*

122. The MARINE study screened 610 patients and randomized 229 patients. DX 1694 (MARINE Study Report) at 6. According to the inclusion criteria, all randomized patients were required to have baseline triglycerides $\geq$ 500 mg/dL and $\leq$ 2,000 mg/dL. DX 1694 (MARINE Study Report) at 31. Continued administration of both "[s]tatins and ezetimibe were permitted as part of the MARINE trial." Miller Dep. Tr. at 222:13-16; DX 1694 (MARINE Study Report) at 30. Patients were further required to be "[w]illing to maintain a stable diet and physical activity level throughout the study." DX 1694 (MARINE Study Report) at 31.

123. "[A]ll patients who qualified for the 12-week MARINE study had severe hypertriglyceridemia." Budoff Tr. 493:19-22. "Patients were given diet and exercise for a period of four to six weeks as a lead-in before the 12-week study began." *Id.* at 491:18-21 (Budoff). "There was then a two- to three-week qualifying period." *Id.* at 491:22-24 (Budoff). In other words, the "screening period [for MARINE] included a 4- or 6-week diet and lifestyle stabilization period and wash out period followed by a 2-week TG qualifying period." DX 1694 (MARINE Study Report) at 27; *see also* Sheinberg Tr. 634:8-14. The purpose of the 2-week qualifying period was to ensure that patients who were included in the study "had severe hypertriglyceridemia that was not addressed by diet and exercise in the four- to six-week lead in." Budoff Tr. 492:4-7. "[S]ome of these patients responded to the dietary instructions they received," and 250 patients did not proceed to randomization because their "average TG levels were not within the range required for inclusion in the study." DX 1694 (MARINE Study Report) at 120.

124. Other patients were excluded for several other reasons. *Id.* at 31-32. For example, "one of the exclusion criteria [was] known familial lipoprotein lipase impairment or deficiency, Fredrickson Type I, apolipoprotein C-II deficiency, and also familial – dysbetalipoproteinemia." Toth Tr. 1890:2-12. Therefore, patients with these genetic conditions for severe hypertriglyceridemia

were excluded from the MARINE study." *Id.* at 1890:13-16 (Toth). This presumably was because Vascepa would not be sufficient to treat patients with these genetic conditions.

125. Thus, "[o]nly patients with triglycerides above 500 after this four to six-week lead-in and the two to three-week qualifying period entered into the 12-week safety and efficacy MARINE trial." Budoff Tr. 492:23-493. And "Vascepa is indicated for those patients who qualified for the MARINE trial." Ketchum Tr. 191:10-12. Likewise, "[D]efendants' labels" are "directed to this patient population." *Id.* at 191:13-15 (Ketchum).

126. At randomization (i.e. after the lead-in periods), the median baseline triglyceride level was 679.5mg/dl. DX 1741 (Bays 2011) at 4. The median baseline LDL-C level of study participants in the MARINE Study was 90.5 mg/dl. *Id.* The median baseline Apo B level was 121.0 mg/dl.. *Id.* The mean baseline body mass index was 30.8 kg/m^2. *Id.*

127. The MARINE Study included two treatment arms, one in which patients were administered 2 g/day of Vascepa® and one in which patients were administered 4 g/day of Vascepa®. *Id*. at 2. A third arm of patients were administered placebo. *Id.* "The subjects in the placebo group in MARINE were instructed to maintain the diet and exercise regimen throughout the entire 12-week period." Budoff Tr. 494:13-16.

128. With respect to the treatment arm that received 4 g/day of Vascepa®, by the end of the study, median triglyceride levels had declined to 502.0 mg/dl, and the average LDL-C and Apo B levels had declined to 86.0 (from 90.5) mg/dl and 117.0 (from 121.0) mg/dl, respectively. DX 1741 (Bays 2011) at 4.

129. In this treatment arm, "MARINE reported the most significant reduction in triglyceride levels at just four weeks." Budoff Tr. 498:24-499:1. More specifically, MARINE showed that Vascepa® 4 g/day reduced patients' triglyceride levels from a median of 679.5 mg/dL to a median of 471.0 mg/dL after only four weeks of drug treatment. DX 1694 (MARINE Study Report) at 214. Thus, "by week four, the median patient had a triglyceride level below 500" mg/dl. Budoff Tr. 499:12-14.

130. While the median LDL-C and Apo-B levels showed a decrease in the treatment arm that received 4 g/day of Vascepa®, a substantial number of patients in the MARINE Study did not

experience a decline in LDL-C or Apo B levels. The MARINE Study reported that in the third quartile of patients in the 4 g treatment arm, there was a 17.2% increase in LDL-C levels at 12 weeks compared to baseline, which was significantly higher than the increase in the placebo arm. *Compare* DX 1694 (MARINE Study Report) at 268 *with* DX 1741 (Bays 2011) at 2; *see also* Sheinberg Tr. 599:3-8. Some patients experienced even greater increases, with at least one patient experiencing a 156% increase. *See* DX 1694 (MARINE Study Report) at 273.

131. Similarly, not all patients in the MARINE Study experienced a drop in Apo B levels in the treatment arm that received 4 g/day of Vascepa®. The MARINE Study reported that in the third quartile of patients in the 4 g treatment arm, there was a 3.8% increase in Apo B levels at 12 weeks compared to baseline. DX 1694 (MARINE Study Report) at 239; *see also* Sheinberg Tr. 599:15-21. And MARINE reported a maximum 41% increase in Apo B levels at 12 weeks compared to baseline in the 4 g treatment arm. *Id.* at 242. Thus, the MARINE Study failed to show that Vascepa® does not increase LDL-C, or that it reduces Apo B, for at least a quarter or more of patients. Only about 29% of the patients enrolled in the 4 g treatment arm of the MARINE Study were diabetics. DX 1741 (Bays 2011) at 2.

132. With respect to the placebo treatment arm, by the end of the study, about one-fifth (21%) of patients reduced their triglyceride levels to below 500 mg/dL with diet and exercise alone. DX 1694 (MARINE Study Report) at 72; *see also* Sheinberg Tr. 635:15-23. In other words, "after 12 weeks of continuing a diet and exercise regimen, 21 percent of those subjects in the placebo group, 16 out of 75, were able to achieve and maintain triglyceride levels below 500 milligrams per deciliter by the study endpoint." Budoff Tr. 494:20-25; *see also* DX 1701 (FDA Medical Review) at 51; Sheinberg Tr. 635:14-23. These patients were able to achieve these triglyceride levels "by continuing to follow the lifestyle modification plan that was set out in the initial evaluation." Sheinberg Tr. 635:21-23.

133. Thus, "according to MARINE, about 21 percent of patients falling within the scope of defendants' indication can achieve and maintain triglyceride levels below 500 with diet and exercise alone." Budoff Tr. 495:3-7. These were patients "who, in the first four to six weeks tried diet and exercise alone and it didn't work," so "if these patients in the placebo group were given Vascepa

immediately, their triglyceride levels would [have] drop[ped] more quickly." *Id.* at 495:16-23 (Budoff).

134. Therefore, the MARINE placebo group confirms that patients with severe hypertriglyceridemia do not require drug therapy for at least 12 weeks to reduce and maintain triglyceride levels below 500 mg/dL. But as explained by Dr. Sheinberg, it took several weeks for these patients to reduce levels below 500 mg/dL with diet and exercise alone, so these patients would benefit from short-term icosapent therapy as an adjunct to diet and exercise to avoid pancreatitis risk when treatment first begins. Sheinberg Tr. 638:4-20. In other words, these patients [could] have benefitted from a short course of Vascepa before diet and exercise took effect to reduce their triglycerides below 500. *Id.* at 636:2-16 (Sheinberg); *see also id.* at 636:17-637:7 (Sheinberg).

3. Labelling for Vascepa and Defendants' ANDA products

a. Duration of treatment

135. Taking Defendants' labels as a whole, from the perspective of a treating physician, Defendants' labels are silent as to duration of therapy—that is, they do not encourage, recommend, promote, instruct, or require administering Defendants' ANDA products to a patient for at least 12 weeks. *See*, *e.g.*, DX 2256 (Hikma Label); DX 2266 (DRL Label). In particular, Defendants' labels contain neither an explicit nor an implicit instruction to administer Defendants' ANDA products for at least 12 weeks.

i. The Indications and Usage section of Defendants' labels does not encourage, recommend, promote, instruct, or require any specific duration of treatment.

136. Where an approved drug product is indicated for a particular or minimum duration of drug treatment, that duration is generally stated in the "Indications and Usage" section, or the "Dosage and Administration" section of the product labeling. Physicians generally look to these sections of drug labeling to determine whether a drug should be administered for a particular duration of time.

137. The Indications and Usage section in Defendants' labela states that their products are indicated "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2.

138. As such, the "Indications and Usage" section of Defendants' labels is silent as to the duration of icosapent drug treatment. More specifically, "[t]he concise indication does not include any limitation, and the usage does not include any limitation with respect to duration of therapy." Peck Tr. 1374:16-20. Therefore, based on the Indications and Usage section, "the approved patient population is bounded by only two characteristics, age and disease condition."[3] *Id.* at 1373:5-11 (Peck).

139. In particular, "[n]either the Vascepa indication nor [D]efendants' indication is actually telling doctors to use the drug for at least 12 weeks." Budoff Tr. 442:15-18. Defendants' ANDA products are indicated solely "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia," without regard to the duration of drug treatment. DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2.

140. Rather, "the Vascepa label, as well as [D]efendants' labels, leave it entirely up to the physician's discretion to determine the duration of treatment." Budoff Tr. 444:8-11; *see also* Sheinberg Tr. 608:14-20, 618:6-14.

141. Moreover, the FDA's "Guidance for Industry" states that the "Indications and Usage" section must set forth the "[s]elected patient subgroups or disease subpopulations for whom the drug is approved." PX 573 at 11. In other words, "the indication should clearly convey the patient population for which the drug is approved." *Id*. If the drug's use is limited to "patients previously treated with other therapies," for example, that limitation must be in the indication. *Id*. In the case of Vascepa, "[t]he FDA-approved labeling does not limit the patient population for whom Vascepa is approved based on prior diet." Peck Tr. 1367:16-22.

142. Amarin is "relying on the term severe hypertriglyceridemia in the indication as signaling to doctors that they should use the drug long-term." Budoff Tr. 454:1-4. But

[3] Earlier versions of the Vascepa label contained a "Usage Considerations" section stating that "Patients should be placed on an appropriate lipid lowering diet and exercise regimen before receiving Vascepa, and should continue this diet and exercise regimen with Vascepa." DX 1698 (Vascepa 2017 Label) at 2; *see also* Peck Tr. 1362:12-22. This "usage consideration statement has been removed from the current Vascepa indication." Peck Tr. 1362:23-1363:1. And "as a result, . . . [D]efendants' labeling . . . do not include this usage consideration statement from the 2017 Vascepa label." *Id.* at 1362:2-6 (Peck).

"[D]efendants' labels never actually say that severe hypertriglyceridemia is a chronic condition." *Id.* at 448:1-4 (Budoff).

143. In fact, Defendants' labels define "severe hypertriglyceridemia" as "≥ 500 mg/dl." DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2. Thus, "as long as the patients have triglyceride [("TG")] levels above 500, regardless of why, they have severe hypertriglyceridemia." Budoff Tr. 455:8-11. And, as discussed, there are acute causes of severe hypertriglyceridemia. FF[4] ¶¶ 91, 95-100.

144. Therefore, "the MARINE indication in the Vascepa label, and the indicated use of icosapent in defendants' labels, is not limited to chronic use." Peck Tr. 1361:8-11. Instead, the "Indications and Usage" section leaves the duration of drug treatment to the discretion of the treating physician.

ii. The Dosage and Administration section of Defendants' labels does not encourage, recommend, promote, instruct, or require any specific duration of treatment.

145. Likewise, "the [D]osage and [A]dministration section in [D]efendants' labels doesn't specify any duration of treatment." Budoff Tr. 442:24-443:2; *see also* Peck Tr. 1377:4-7. "[I]n fact, neither the [I]ndication nor the [D]osage and [A]dministration sections of [D]efendants' labels in any way limits the duration of treatment." *Id.* at 1377:8-11 (Peck).

146. In contrast to Defendants' labels, the "Dosage and Administration" sections of labels for drugs that are indicated for particular or minimum durations state such durations expressly.

147. For example, the "Dosage and Administration" section of the label for Lamisil (terbinafine hydrochloride) tablets instructs that the drug should be administered "once daily for 6 weeks" to treat fingernail onychomycosis, and "once daily for 12 weeks" to treat toenail onychomycosis. DX 1984 (Lamisil Label) at 2; *see also* Sheinberg Tr. 610:4-15. Similarly, the "Dosage and Administration" section of the label for Lovenox (enoxaparin sodium injection) states: "Continue Lovenox for a minimum of 5 days." DX 1679 (Lovenox Label) at 5; *see also* Sheinberg

[4] "FF" refers to Defendants' proposed post-trial findings of fact set forth in this document.

Tr. 611:4-13. Conversely, the "Dosage and Administration" section of Defendants' labels contain no such instructions. DX 2256 (Hikma Label) at 2; DX 2266 (DRL Label) at 2.

148. In addition to being silent in terms of duration, the Dosage and Administration section of Defendants' labels also does not instruct doctors to rule out all reversible causes before treating a patient with Vascepa.

149. Section 2.1 of the Dosage and Administration section of Defendants' labels says to "[a]ssess lipid levels before initiating therapy." DX 2256 (Hikma Label) at 2; DX 2266 (DRL Label) at 2. This "makes sense" that a patient would "have to take a test" to assess lipid levels before being placed on a therapy. Budoff Tr. 469:20-24. This is "standard" language. *Id.* (Budoff).

150. In the same bullet, the label says to "identify other causes, e.g. diabetes, hypothyroidism, or medications of high triglyceride levels, and manage as appropriate." DX 2256 (Hikma Label) at 2; DX 2266 (DRL Label) at 2. "[T]he label leaves it up to the discretion of the doctor to manage as the doctor feels is appropriate." Budoff Tr. 470:7-10. In this bullet, "the label is not telling doctors don't give icosapent yet, address those other factors first." *Id.* at 470:11-14 (Budoff). "And the bullet certainly isn't saying only give icosapent if absolutely necessary and the only causes are genetics." *Id.* at 470:15-18 (Budoff). Instead, the wording gives "doctors wide discretion to do what the doctor sees fit for the individual patient." *Id.* at 470:19-22 (Budoff).

151. The second bullet in section 2.1 of the Dosage and Administration section says that "patients should engage in nutritional intake and physical activity before receiving icosapent ethyl which should continue during treatment with icosapent ethyl." DX 2256 (Hikma Label) at 2; DX 2266 (DRL Label) at 2. This is "[t]he only statement as to timing in the [D]osage and [A]dministration section." Peck Tr. 1377:12-19. And this language does not instruct doctors to rule out all reversible causes before treating a patient with Vascepa. Sheinberg Tr. 605:7-16; *see also id.* at 607:10-608:1 (Sheinberg).

152. First, "[t]he term 'should' [in this bullet of section 2.1] implies a recommendation to the doctor, but it doesn't limit the doctor to a particular action." Peck Tr. 1377:21-24. More specifically, "when FDA uses the term 'should' in a pharmaceutical label, it is leaving certain actions to the wide discretion of the physician." *Id.* at 1378:20-23 (Peck).

153. Second, the phrase "'patients should engage in appropriate nutritional intake and physical activity before receiving icosapent,' does not state how long diet and exercise should precede the prescription." *Id.* at 1379:25-1380:6 (Peck). And "engaged in appropriate nutritional intake" is "a combination of both" beginning healthy habits and restraining from other unhealthy habits. Sheinberg Tr. 608:21-609:10. This bullet in section 2.1 "is leaving the nutritional intake and physical activity for a particular patient up to the discretion of the doctor." Peck Tr. 1379:13-17.

154. Thus, this phrase comports with the clinical reality that diet modifications often involve ceasing conduct, such as stopping the intake of excess alcohol or sugars. Sheinberg Tr. 608:21-609:14. Other examples include "[d]iscontinuation of sugared beverages, discontinuation of alcohol, [and] discontinuation of tobacco products." *Id.* at 704:11-13 (Sheinberg).

155. Additionally, the phrase comports with the clinical reality that "[i]f a patient that is at risk for [a] potential life-threatening complication [(in this case acute pancreatitis)], [doctors] treat that person aggressively from day one." *Id.* at 568:19-23 (Sheinberg); *see also id.* at 607:10-23, 636:17-637:7 (Sheinberg).

156. "To be clear, the [D]osage and [A]dministration section of [D]efendants' labels does not require doctors to wait and see if patients fail to maintain triglycerides below 500 milligrams per deciliter with diet and exercise before prescribing icosapent." Peck Tr. at 1381:13-18; *see also* Sheinberg Tr. 605:17-607:7. Instead, treatment guidelines "advise that clinicians immediately treat severely hypertriglyceridemic patients with triglyceride lowering drugs." Budoff Tr. 479:12-22.

157. "If FDA had determined that safety or efficacy concerns required pretreatment diet changes or stabilization prior for a particular period of time, it would have so stated in the labeling." Peck Tr. 1383:1-7. In other words, if there was "a reason to narrow the patient population until after some initial treatment by a different treatment, the label would say that." *Id.* at 1387:5-8 (Peck). "For example, the [D]osage and [A]dministration section of the labeling for Alimta instructs that physicians must initiate folic acid pretreatment for a full seven days before the first dose of Alimta to avoid increased risk of myelosuppression, i.e., bone marrow suppression." *Id.* at 1386:11-17 (Peck). This is not the case with Defendants' labels, or with the Vascepa label.

158. For these reasons, looking at "the [I]ndications and [U]sage section and the [D]osage and [A]dministration section, neither section specifies any specific treatment duration." *Id.* at 1388:20-23 (Peck). Moreover, neither section requires that a doctor have a patient try and fail with diet and exercise before beginning Vascepa, such that all reversible cases of severe hypertriglyceridemia would be excluded from Vascepa treatment. Sheinberg Tr. 605:7-16.

iii. The Clinical Studies section of Defendants' labels does not encourage, recommend, promote, instruct, or require any specific duration of treatment.

159. Under FDA regulations, "other sections of the labeling cannot imply or suggest alternative dosing regimens not stated in the [D]osage and [A]dministration section." Peck Tr. 1388:20-1389:3. Moreover, "you must not imply or suggest indications or uses or dosing regimens not stated in the [I]ndications and [U]sage or [D]osage and [A]dministration section from the [C]linical [S]tudy section." *Id.* at 1404:19-25 (Peck); *see also* 21 C.F.R. § 201.57(c)(15). Even if other sections could imply or suggest dosing regimens, no other section of Defendants' labels instructs a physician to use Vascepa for any certain duration.

160. For example, "the clinical trial studies section of [D]efendants' labels does not say, doctors, you should give the drug for at least 12 weeks." Budoff Tr. 444:2-7.

161. The "Clinical Studies" section of both Defendants' labels describes a clinical study and states that "[p]atients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks." DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 8-9; *see also* Sheinberg Tr. 613:3-8.

162. This is the only reference in Defendants' labels to administering EPA for at least 12 weeks, and it is merely a description of the length of the clinical trial (sometimes referred to as the MARINE study) that supported approval of the Vascepa indication for treating severe hypertriglyceridemia. "[W]hat [D]efendants' labels are doing in section 14.2 [(the Clinical Studies section)] are describing the MARINE study which lasted 12 weeks." Peck Tr. 1405:24-1406:1.

163. But one "can't reasonably read [section] 14.2 of [D]efendants' label as saying, okay, the study was 12 weeks, therefore doctors should prescribe the drug for 12 weeks, no less, no more." *Id.* at 1406:6-10 (Peck). "[T]he fact that . . .the clinical study discussed in the [C]linical [S]tudy

section lasted for 12 weeks is informing doctors that icosapent can be used for at least 12 weeks, . . . [b]ut a doctor would know from the label as a whole that icosapent also can be used for shorter or longer durations." *Id.* at 1406:12-21 (Peck). "The doctor has discretion to use the drug for as long as he thinks is in the best interest of the patient absent a limitation." *Id.* (Peck). And, as discussed above, Defendants' labels contain no such limitation.

164. Furthermore, "some physicians will find some of the clinical study information helpful, but others will find it irrelevant to their practices." Budoff Tr. 503:2-5. In fact, "some of the data may be completely irrelevant to a prescribing physician." *Id.* at 502:24-503:1 (Budoff).

165. "[D]efendants' labels don't otherwise comment on the 12-week duration such as saying because these effects were achieved in 12 weeks, make sure you give the drug for at least 12 weeks." *Id.* at 504:9-13 (Budoff).

166. And, again, with respect to the information in the Clinical Studies section, the FDA regulations state that "you must not imply or suggest indications or uses or dosing regimens not stated in the [I]ndications and [U]sage or [D]osage and [A]dministration section from the [C]linical [S]tudy section." Peck Tr. 1404:19-25; *see also* 21 C.F.R. 201.57(c)(15). Thus, "the length of a clinical study reported in the [C]linical [S]tudy section is not supposed to imply or suggest a particular dosing regimen that's not stated in the [D]osage and [A]dministration section." Peck Tr. 1405:19-23.

iv. The remaining sections of Defendants' labels do not encourage, recommend, promote, instruct, or require any specific duration of treatment.

167. Looking at the remaining sections of Defendants' labels, the "Adverse Reactions" and "Clinical Pharmacology" sections of Defendants' labels similarly refer to the same 12-week clinical study. *See* DX 2256 (Hikma Label) at 3 ("In two randomized, double-blind, placebo-controlled trials in patients with triglyceride levels between 200 and 2000 mg/dL treated for 12 weeks, adverse reactions reported with icosapent ethyl at an incidence ≥1% more frequent than placebo based on pooled data included arthralgia and oropharyngeal pain."); DX 2266 (DRL Label) at 3 (same); DX 2256 (Hikma Label) at 5 ("In a 12-week, dose-ranging study in patients with severe hypertriglyceridemia icosapent ethyl 4 grams per day reduced median TG from baseline relative to placebo [*see Clinical Studies (14)*]."); DX 2266 (DRL Label) at 6 (same). "[T]hese 12-week

durations simply describe what was seen in these limited studies, it does not in any way indicate to [doctors] that that is how long [doctors] need to treat [their] patients for." Sheinberg Tr. 614:18-21.

168. These statements in Defendants' labels are not instructions to administer Defendants' ANDA products for any duration, let alone for at least 12 weeks. Under FDA regulations, "[i]ndications or uses must not be implied or suggested in other sections of the labeling if not included" in the "Indications and usage" section. 21 C.F.R. § 201.57(c)(2)(iv).

169. The "Patient Information" section of Defendants' labels also does not encourage any particular treatment duration, much less a treatment duration of at least 12 weeks. Amarin points to an instruction that states: "Do not change your dose or stop taking icosapent ethyl without talking to your doctor." DX 2256 (Hikma Label) at 9; DX 1974 (DRL Label) at 11. "This statement is not instructing doctors and patients [t]o use icosapent for at least 12 weeks." Budoff Tr. 505:23-25; *see also* Sheinberg Tr. 614:25-615:10. "In fact, this statement doesn't speak to whether the label is encouraging any particular duration." Budoff Tr. 505:1-4. Instead, "[t]he statement just warns [a patient] if you're going to stop it, talk to your doctor." *Id.* (Budoff).

170. In other words, this is not an instruction to administer Defendants' ANDA products for any duration, let alone for at least 12 weeks. This statement does not specify when patients should "talk[]" to their doctor, or what the doctor should say. The statement is consistent, for example, with a patient "talking" to her doctor after only 8 weeks, and with the doctor telling the patient that she should "stop taking" the drug at that time. *Id.* at 497:15-20 (Budoff); Sheinberg Tr. 615:11-19.

171. Finally, the preclinical studies discussed in Defendants' labels do not encourage any particular treatment duration. Two of these studies were longer than 12 weeks—one being 2 years long and the other being 6-months long. DX 2256 (Hikma Label) at 7; DX 2266 (DRL Label) at 7 ("In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl . . . ."); *id.* at 8 ("In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl . . . .").

172. By contrast, two other rat studies described in this section were for shorter than 12 weeks—one being 9 weeks and one being 14 days. *Id.* ("In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to

female rats for 14 days before mating through day 7 of gestation . . . ."); DX 2256 (Hikma Label) at 7 (same).

173. None of these preclinical studies involved treating a subject with triglycerides of at least 500 mg/dL by administering a daily dose of 4 g EPA, as required by every asserted claim. Thus, these statements are not even descriptions of the claimed method of use, let alone instructions to perform that method. DX 2256 (Hikma Label) at 7; DX 2266 (DRL Label) at 7-8.

v. The Defendants' labels taken as a whole do not encourage, recommend, promote, instruct, or require any specific duration of treatment.

174. All experts testifying on the issue of infringement agreed that "the Vascepa label, as well as [D]efendants' labels, leave it entirely up to the physician's discretion to determine the duration of treatment." Budoff Tr. 444:8-11; *see also* Peck Tr. 1389:7-14; Sheinberg Tr. 608:14-20, 618:6-14. "[D]efendants' labels will allow doctors to tailor treatment duration to the individual patients." Budoff Tr. 444:12-16. Thus, there is no instruction anywhere in Defendants' labels to administer Defendants' ANDA products to a patient for any duration, let alone for at least 12 weeks. As a whole, Defendants' labels are indifferent to the duration of drug treatment.

175. Additionally, all experts testifying on the issue of infringement agreed that the Defendants' labels cover use of icosapent for less than 12 weeks, in addition to at least 12 weeks. In other words, "it would be entirely consistent with [D]efendants' labels for a doctor to prescribe icosapent for less than 12 weeks." Budoff Tr. 445:5-8. "[T]o be clear, there's no statement anywhere in [D]efendants' labels requiring doctors to use icosapent for at least 12 weeks." Peck Tr. 1390:1-4. "The labels are completely silent in this regard, and therefore [ ] it is left up [to] the discretion of the prescribing physician." Sheinberg Tr. 618:12-14.

176. All experts testifying on the issue of infringement also agreed that the label as a whole expresses no preference for any treatment duration. "[D]efendants' labels never say that icosapent is safe and effective only if administered for at least 12 weeks." Peck Tr. 1390:20-24. Rather, there is "no minimum or maximum therapy duration anywhere in [D]efendants' labels." *Id.* at 1389:12-14 (Peck); *see also* Sheinberg Tr. at 618:6-14.

177. Relatedly, "[D]efendants' labels as a whole allow[] physicians to exercise their discretion as to both the timing and content of any diet counseling." Peck Tr. 1389:7-11. "The label is leaving the nutritional intake and physical activity for a particular patient up to the discretion of the doctor." *Id*. at 1379:13-17 (Peck).

178. Moreover, "[D]efendants' labels never mention a genetic component associated with severe hypertriglyceridemia." *Id.* at 1390:25-1391:3 (Peck). And the label as a whole does not imply or suggest that severe hypertriglyceridemia is a chronic condition. "[D]efendants' labels never actually say that severe hypertriglyceridemia is a chronic condition." Budoff Tr. 448:1-4. Again, "there was a proposal to the FDA from Amarin to characterize the Vascepa patient population as requiring chronic case, but FDA rejected" the proposal. *Id.* at 448:8-11 (Budoff); *Compare* DX 2248 (Vascepa Label) *with* DX 2247 (Vascepa Proposed Label).

179. In short, Defendants' labels do not explicitly or implicitly instruct or encourage physicians to administer Defendants' ANDA products to a patient for at least 12 weeks. *See generally* DX 2256 (Hikma Label); DX 2266 (DRL Label).

b. Concurrent lipid-altering therapy

180. Beyond requiring drug treatment for at least 12 weeks and requiring specific lipid effects, three asserted claims further require that the patient does "not receive concurrent lipid altering therapy." *See* DX 1500 ('728 patent claims 1 and 16); DX 1502 ('715 patent claim 14). Defendants' labels do not encourage use of icosapent with or without a concurrent lipid-altering therapy. Instead, the label is indifferent.

181. "[A] statin is an example of a lipid-altering therapy." Budoff Tr. 520:13-15. Thus, "concurrent lipid altering therapy" includes, but is not limited to, statins. There are other drugs besides statins that are also concurrent lipid altering therapies, e.g., fibrates, niacin, and ezetimibe. *Id.* at 520:18-25; *see also* Sheinberg Tr. 645:16-21. Plaintiffs' claim construction expert, Dr. Miller, agreed, for example, that "ezetimibe is not a statin," but "ezetimibe would also be considered a concomitant lipid-altering therapy." Miller Dep. Tr. at 208:9-16.

182. All of the experts testifying on the issue of infringement agreed that the Defendants labeling expresses no preference on whether the drug is taken with or without concurrent lipid altering

therapy. *E.g.*, Budoff Tr. 521:4-7, 523:7-13, 523:21-24; Peck Tr. 1412:7-10; Sheinberg Tr. 647:22-25.

183. The Defendants' labeling and the "Vascepa labeling [is not read] as requiring doctors . . . to give the drug without a statin." Budoff Tr. 521:4-7. In fact, "there's nothing in the . . . label as a whole suggesting any preference for using icosapent with or without a statin." *Id.* at 523:7-13 (Budoff).

184. "[T]he [D]efendants' labeling leaves it entirely up to the physician's discretion as to whether to add a concurrent lipid-altering therapy to icosapent." *Id.* at 523:21-25 (Budoff). "If [the concurrent lipid-altering therapy] [is] needed [the physician] add[s] it, if it's not needed, [the physician] [doesn't] have to add it." *Id.* at 523:24-25 (Budoff); *see also* Sheinberg Tr. 647:22-25.

185. The "Clinical Studies" section of Defendants' labels states that "[t]wenty-five percent of patients were on concomitant statin therapy." DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 8-9. This statement "is just letting doctors know that 25 percent of patients in the clinical study discussed in the labeling were taking a statin." Budoff Tr. 521:23-522:1. This statement "is not an instruction to doctors to make sure they use a statin." *Id.* at 522:5-7 (Budoff). It is "not a mandate to use a statin in this indication . . . [a]nd it's not mandating not to use a statin either." *Id.* at 522:5-9 (Budoff). Thus, "[y]ou have the option as a physician to use [the drug] with or without a statin." *Id.* at 521:6-7 (Budoff).

186. "And this statement doesn't say anything about other lipid-altering therapies." *Id.* at 522:10-12 (Budoff). In other words, the fact that 25% of patients were on concomitant statin therapy does not mean that the remaining 75% of patients avoided taking other lipid altering therapies. In fact, "the labeling doesn't say anything about whether this 75 percent of patients were taking a different lipid-altering therapy." *Id.* at 522:22-25 (Budoff); *see also* Sheinberg Tr. 647:13-16. There is no statement in Defendants' labels regarding whether the patients in the reported clinical trial were on concurrent lipid altering therapy, or not.

187. Regardless, the statement in Defendants' labels that "[t]wenty-five percent of patients were on concomitant statin therapy" shows that Defendants' ANDA products are suitable for the substantial noninfringing use of treating a patient with severe hypertriglyceridemia who is on

concurrent lipid altering therapy. DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 8. That use of Defendants' ANDA products would not be unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental.

188. The "Clinical Pharmacology" section of Defendants' labels reports studies on "Drug-Drug Interactions" between EPA and various concurrently administered drugs. DX 2256 (Hikma Label) at 5-7; DX 2266 (DRL Label) at 6-7. This section states that EPA did not change the pharmacokinetics or blood levels of "atorvastatin," which is a statin. DX 2256 (Hikma Label) at 7; DX 2266 (DRL Label) at 7. Physicians would understand these statements to confirm that Defendants' ANDA products can safely be co-administered with a concurrent lipid altering therapy. Sheinberg Tr. 646:24-647:4.

189. Taken as a whole, Defendants' labels are indifferent to whether a patient to whom Defendants' ANDA products are administered is on concurrent lipid altering therapy. *Id.* at 647:22-25 (Sheinberg). The labels do not "express any preference either way." *Id.* (Sheinberg). In fact, there is no information in the label even describing the use of icosapent without a concurrent lipid altering therapy, much less encouraging the claimed treatment. *Id.* at 647:13-21 (Sheinberg). Therefore, Defendants' labels do not explicitly or implicitly instruct physicians to administer Defendants' ANDA products to a patient who is not on concurrent lipid altering therapy.

c. The labeling does not encourage use of icosapent to achieve the claimed lipid effects

190. Beyond requiring drug treatment for at least 12 weeks, nine of the 10 asserted claims further require at least one of the following effects: (a) a reduction in triglycerides that is "statistically significant" or "of at least about" 10% or 20% (DX 1502 ('715 patent claim 14); DX 1514 ('560 patent claims 4 and 17)); (b) no increase, no "substantial[]" increase, no "statistically significant" increase, or no "more than 5%" increase in LDL-C levels (DX 1500 ('728 patent claim 1 and 16); DX 1502 ('715 patent claim 14); DX 1504 ('677 patent claim 1 and 8); DX 1506 ('652 patent claim 1); DX 1514 ('560 patent claim 4 and 17)); or (c) a reduction in "apolipoprotein B" (DX 1502 ('715 patent claim 14); DX 1504 ('677 patent claim 8); DX 1516 ('929 patent claim 5)).

i. The labeling does not encourage use of icosapent to achieve the claimed triglyceride effect

191. Three of the 10 asserted claims require a reduction in triglycerides that is "statistically significant" or "of at least about" 10% or 20%. DX 1502 ('715 patent claim 14); DX 1514 ('560 patent claims 4 and 17). Defendants' labels do not encourage the use of icosapent to achieve this claimed triglyceride effect.

192. The "Indications and Usage" section of Defendants' labels states that Defendants' ANDA products are indicated solely "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia," without regard to the degree of triglyceride reduction. DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2. Thus, "[D]efendants' products are not indicated specifically to reduce triglycerides by any particular amount." Budoff Tr. 519:23-25.

193. Likewise, the "Dosage and Administration" section of Defendants' labels refers only to treating "high triglyceride levels," without any reference to the claimed minimum amounts of triglyceride reductions. DX 2256 (Hikma Label) at 1-2; DX 2266 (DRL Label) at 2.

194. The only mention of the claimed triglyceride effect in Defendants' labels is in the "Clinical Studies" section. That section includes a table (Table 2) that reports only the "median" triglyceride changes reported for a clinical study in which 76 patients were treated with 4 g/day of Vascepa. DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9. "And median data from a clinical trial may or may not relate to an individual patient depending on, for example, the specific patient population that was being tested." Budoff Tr. 512:6-12. Thus, the median result reported for the reduction in TGs does not represent changes or effects that all persons in the study experienced. Additionally, doctors may not find median data "helpful," because they instead "need to know how many patients were above and below" the median. Toth Tr. 1818:2-7.

195. Under Table 2, the Clinical Studies section states that "[i]cosapent ethyl 4 grams per day reduced median TG . . . levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9. This statement is simply "reporting on

observations concerning the clinical trial that's being reported in table 2." Budoff Tr. 511:9-12. "[T]hese are not instructions on how to use icosapent." *Id.* at 511:13-15 (Budoff).

196. For the reasons stated above, neither these statements, nor the data in Table 2 on which they are based, are explicit or implicit instructions to administer Defendants' ANDA products to achieve the claimed TG effect. *Id.* at 511:13-15 (Budoff). At most, these statements and data merely describe the fact that the claimed lipid effects were reported in certain patients in a clinical study, as reflected in the median data. DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 8-9.

197. More specifically, MARINE shows that at least 25%, and likely more, patients taking Vascepa do not experience any reduction in triglycerides, let alone the claimed minimum amounts. DX 1694 (MARINE Study Report) at 214 (showing that the percent change in triglycerides for the third quartile of patients was 0.0%).

198. There is no real dispute that Defendants' ANDA products could be used in accordance with their proposed labels without achieving the claimed triglyceride effect. Amarin's own MARINE study explicitly establishes that some patients will not obtain the triglyceride effects required by these claims. Such uses would not be unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental. Thus, as the Court previously held, Defendants' ANDA products are suitable for the substantial noninfringing uses of treating patients with severe hypertriglyceridemia without achieving the claimed lipid effects. ECF No. 278 at 13 n.6.

199. In sum, taken as a whole, Defendants' labels are indifferent to whether the claimed TG effect is achieved in patients who are administered Defendants' ANDA products. *See generally* DX 2256 (Hikma Label); DX 2266 (DRL Label). That is, Defendants' labels do not explicitly or implicitly instruct physicians to administer Defendants' ANDA products to a patient to achieve the claimed triglyceride effect. Budoff Tr. 511:13-15.

ii. The labeling does not encourage use of icosapent to achieve the claimed LDL-C effect

200. Likewise, the Defendants' labels do not encourage use of icosapent to achieve the claimed LDL-C effects. Eight of the 10 asserted claims require no increase, no "substantial[]" increase, no "statistically significant" increase, or no "more than 5%" increase in LDL-C levels.[5]

201. The "Indications and Usage" section of Defendants' labels states that Defendants' ANDA products are indicated solely "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia," without regard to whether that reduction is accompanied by an increase in LDL-C. DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2. Thus, "Defendants' products are not indicated to control LDL-C." Budoff Tr. 513:3-5.

202. In contrast, some drugs are specifically indicated for controlling LDL-C levels. For example, Lipitor is indicated "as an adjunct to diet to reduce elevated total-C, LDL-C, [A]po B, and TG levels and to increase HDL-C in adult patients with primary hypercholesterolemia . . . and mixed dyslipidemia." DX 1986 (current Lipitor label) at 3; *see also* DX 3007 (2007 Lipitor label) at 14. Conversely, the indication in Defendants' labels is silent with regard to LDL-C. DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2.

203. Likewise, the "Dosage and Administration" section of Defendants' labels refers only to treating "high triglyceride levels," without any reference to whether the drug increases LDL-C. DX 2256 (Hikma Label) at 1-2; DX 2266 (DRL Label) at 2.

204. The only mention of the claimed LDL-C effect in Defendants' labels is in the "Clinical Studies" section. That section includes a table (Table 2) that reports only the "median" changes reported for a clinical study in which 76 patients were treated with 4 g/day of Vascepa. DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9. "And median data from a clinical trial may or may not relate to an individual patient depending on, for example, the specific patient population that was being tested." Budoff Tr. 512:6-12.

[5] '728 patent claim 1 and 16; '715 patent claim 14; '677 patent claim 1 and 8; '652 patent claim 1; '560 patent claim 4 and 17.

205. Thus, the median results reported for the change in LDL-C levels do not represent changes or effects that all persons in the study experienced. *Id.* (Budoff); *see also* Sheinberg Tr. 642:19-23. Rather, many or even most patients may experience very different results than the reported median values. Budoff Tr. 512:6-9; *see also* Sheinberg Tr. 642:11-18. Physicians thus understand that median results reported for a clinical study may not be achieved when treating an individual patient. Budoff Tr. 512:6-9; *see also* Sheinberg Tr. 643:11-15.

206. Additionally, doctors may not find median data "helpful," because they instead "need to know how many patients were above and below" the median. Toth Tr. 1818:2-7. For example, a "doctor would understand from table 2 and the statement below it . . . that there was no LDL-C increase for an average patient." Budoff Tr. 513:21-24.

207. In fact, table 2 in the Clinical Studies section makes clear that, for some patients, LDL-C is increased. *See* DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9. More specifically, table 2 reports a median LDL-C change relative to placebo of "-2 (-13, +8)," where "+8" represents patients in the study whose LDL-C increased.

208. "[T]he plus eight means that within the group representing 95 percent of the patients in the study, LDL-C increased as high as eight percent." Budoff Tr. 514:16-19. An increase of eight percent is "a clinically meaningful increase." *Id.* at 514:20-22 (Budoff). Thus, a "doctor reading [D]efendants' label[s] would understand that some percentage of patients in this study actually had an LDL-C increase." *Id.* at 514:23-515:2 (Budoff). A "doctor would understand that some patients taking icosapent will actually experience a clinically significant LDL-C increase." *Id.* at 515:3-8 (Budoff).

209. Under Table 2, the Clinical Studies section states that "[i]cosapent ethyl 4 grams per day reduced median . . . VLDL-C . . . levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9.

210. This statement is simply "reporting on observations concerning the clinical trial that's being reported in table 2." Budoff Tr. 511:9-12. "[T]hese are not instructions on how to use icosapent." *Id.* at 511:13-15 (Budoff).

211. Plaintiffs' expert agrees that, with regards to LDL-C, the statement below table 2 in "[Defendants'] label[s] would carry significance to a doctor only because and if the doctor understood that Lovaza had this side effect" of increasing LDL-C. *Id.* at 516:15-18 (Budoff). Without this comparison, "it wouldn't mean much to the doctor to say there was no LDL-C increase." *Id.* at 516:19-21 (Budoff). Defendants' labels do not cross-reference the Lovaza label or otherwise mention Lovaza or its reported side effect of increasing LDL-C. Instead, "Defendants' labels never tell doctors to compare the icosapent clinical trial to the Lovaza clinical trial." *Id.* at 516:22-24 (Budoff).

212. In fact, the "Adverse Reactions" section of Defendants' labels cautions physicians *not* to compare the rates of side effects between different clinical trials for different drugs, and *not* to expect that the reported results of a clinical trial will necessarily be seen in clinical practice: "[b]ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice." *Id.* at 517:9-15 (Budoff); *see also* DX 2256 (Hikma Label) at 3; DX 2266 (DRL Label) at 3. "In other words, [D]efendants' labels [are] telling doctors and warning them against comparing adverse reactions from two clinical trials involving 2 different drugs." Budoff Tr. 517:16-19. Thus, a "doctor reading defendants' labels would understand that two clinical trials involving two different drugs are conducted under different situations, and they may or may not be comparable." *Id.* at 518:3-7 (Budoff).

213. MARINE shows that at least 25%, and likely more, patients taking Vascepa experience an increase in LDL-C that is greater than 5%. DX 1694 (MARINE Study Report) at 239 (showing that the percent change in LDL-C for the third quartile of patients was an increase of 17.2%).

214. There is no real dispute that Defendants' ANDA products could be used in accordance with their proposed labels without achieving the claimed LDL-C effect. Amarin's own MARINE study explicitly establishes that some patients will not obtain the LDL-C effects required by the claims. Such uses would not be unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental. Thus, as the Court previously held, Defendants' ANDA products are suitable for the

substantial noninfringing uses of treating patients with severe hypertriglyceridemia without achieving the claimed lipid effects. ECF No. 278 at 13 n.6.

215. In sum, taken as a whole, Defendants' labels are indifferent to whether the claimed LDL-C effects are achieved in patients who are administered Defendants' ANDA products. Sheinberg Tr. 640:11-18; *id.* at 644:25-645:2 (Sheinberg). That is, Defendants' labels do not explicitly or implicitly instruct physicians to administer Defendants' ANDA products to a patient to achieve the claimed LDL-C effects. *Id.* at 640:11-18 (Sheinberg); *id.* at 644:25-645:2 (Sheinberg).

iii. The labeling does not encourage use of icosapent to achieve the claimed Apo B effect

216. Similarly, the Defendants' labels do not encourage the use of icosapent to achieve the claimed Apo B effect. Three out of 10 claims require a reduction in "apolipoprotein B." DX 1502 ('715 patent claim 14); DX 1504 ('677 patent claim 8); DX 1516 ('929 patent claim 5).

217. The "Indications and Usage" section of Defendants' labels states that Defendants' ANDA products are indicated solely "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia," without regard to whether that reduction is accompanied by a reduction in Apo B. DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2. Thus, "[D]efendants' "indication doesn't mention . . . the term [A]po B." Peck Tr. 1408:1-3.

218. In fact, Amarin previously sought FDA approval for an indication for Vascepa to reduce Apo B, but FDA rejected that indication. DX 1558 at 1 FDA Complete Response; Ketchum Tr. 230:9-14. And Amarin's new Vascepa indication does not address reducing Apo B. Thus, reducing Apo B is not an FDA-approved use of Vascepa, or Defendants' ANDA products. *See* DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2.

219. In contrast, some drugs are specifically indicated for controlling Apo B levels. For example, Lipitor is indicated "as an adjunct to diet to reduce elevated total-C, LDL-C, *apo B*, and TG levels and to increase HDL-C in adult patients with primary hypercholesterolemia . . . and mixed dyslipidemia." DX 1986 (current Lipitor label) at 3 (emphasis added). Conversely, the indication in Defendants' labels is silent with regard to Apo B. DX 2256 (Hikma Label) at 1; DX 2266 (DRL Label) at 2.

220. Likewise, the "Dosage and Administration" section of Defendants' labels refers only to treating "high triglyceride levels," without any reference to whether the drug reduces Apo B. DX 2256 (Hikma Label) at 1-2; DX 2266 (DRL Label) at 2.

221. The only mention of the claimed Apo B effect in Defendants' labels is in the "Clinical Studies" section. That section includes a table (Table 2) that reports only the "median" changes reported for a clinical study in which 76 patients were treated with 4 g/day of Vascepa. DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9. "And median data from a clinical trial may or may not relate to an individual patient depending on, for example, the specific patient population that was being tested." Budoff Tr. 512:6-12.

222. Thus, the median results reported for the reduction in Apo-B do not represent changes or effects that all persons in the study experienced. *Id.* (Budoff); *see also* Sheinberg Tr. 642:19-23. Rather, many or even most patients may experience very different results than the reported median values. Budoff Tr. 512:6-9; *see also* Sheinberg Tr. 642:11-18. Physicians thus understand that median results reported for a clinical study may not be achieved when treating an individual patient. Budoff Tr. 512:6-9; *see also* Sheinberg Tr. 643:11-15.

223. Additionally, doctors may not find median data "helpful," because they instead "need to know how many patients were above and below" the median. Toth Tr. 1818:2-7.

224. Under Table 2, the Clinical Studies section states that "[i]cosapent ethyl 4 grams per day reduced median . . . Apo B levels from baseline relative to placebo." DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9.

225. This statement is simply "reporting on observations concerning the clinical trial that's being reported in table 2." Budoff Tr. 511:9-12. "[T]hese are not instructions on how to use icosapent." *Id.* at 511:13-15 (Budoff). In fact, Dr. Budoff admitted that in his own practice he does not "often measure [Apo B]" levels. *Id.* at 519:14-15 (Budoff). When he prescribes Vascepa, "reducing [A]po B is not an intended result with regard to treating severe hypertriglyceridemia." *Id.* at 519:19-22 (Budoff).

226. Similarly, "[A]po B is not typically monitored and is not a target for therapy in diabetic patients with very high triglycerides." Fisher Tr. 976:12-14.

227. MARINE shows that at least 25%, and likely more, patients taking Vascepa experience no reduction in Apo B, and in fact experience an increase in Apo B. DX 1694 (MARINE Study Report) at 268 (showing that the percent change in Apo B for the third quartile of patients was an increase of 3.8%).

228. There is no real dispute that Defendants' ANDA products could be used in accordance with their proposed labels without achieving the claimed Apo B effects. Amarin's own MARINE study explicitly establishes that some patients will not obtain the lipid effects required by these claims. Such uses would not be unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental. Thus, as the Court previously held, Defendants' ANDA products are suitable for the substantial noninfringing uses of treating patients with severe hypertriglyceridemia without achieving the claimed lipid effects. ECF No. 278 at 13 n.6.

229. In sum, taken as a whole, Defendants' labels are indifferent to whether the claimed lipid effects are achieved in patients who are administered Defendants' ANDA products. That is, Defendants' labels do not explicitly or implicitly instruct physicians to administer Defendants' ANDA products to a patient to achieve the claimed lipid effects. Sheinberg Tr. 640:11-18; *id.* at 644:25-645:2 (Sheinberg).

F. Facts relevant to invalidity

1. Priority date

230. Plaintiffs allege that the asserted claims are "entitled to a priority date of no later than March 2008." ECF No. 331 at ¶ 23. According to Plaintiffs, the named inventors "conceived of the inventions disclosed in the Asserted Claims by March 25, 2008," which they "diligently reduced to practice" through submissions to the FDA and the filing of a provisional application on February 10, 2009. *Id.* at ¶ 24-25.

231. The earliest filing date on the face of Plaintiffs' asserted patents (which are all substantively identical) is February 10, 2009. *See* DX 1500; DX 1502; DX 1504; DX 1506; DX 1514; DX 1516. Plaintiffs have not shown that the named inventors conceived of the claimed inventions by March 25, 2008, and the asserted claims are not entitled to a priority date earlier than February 10, 2009.

a. Background relevant to Plaintiffs' alleged conception date.

232. Before the alleged conception date, Amarin and Laxdale—a company that Amarin acquired in 2004—investigated the efficacy of EPA for Huntington's disease, Schizophrenia, and depression. DX 1814 at 2; Manku Dep. Tr. at 24:22-25:2, 31:10-18. Upon acquiring Laxdale, Amarin focused solely on studying the use of EPA for Huntington's disease. Manku Dep. Tr. at 32:9-12.

233. Around early 2007, however, Amarin's Phase III studies on the use of purified EPA to treat Huntington's disease failed, and FDA refused to grant approval for this indication. *Id.* at 32:25-33:4, 33:6-34:1 (Manku). As a result, Amarin was left with "a huge supply of EPA" and started "studying the use of ethyl-EPA for the treatment of cardiovascular disorders." *Id.* (Manku).

234. In late 2007 and early 2008, an Amarin employee named Mehar Manku made "contact with a scientist in Mochida to ask for their view of differences between pure EPA and EPA/DHA." DX 1883 at 3; *see also* DX 1881 at 8 (stating that as of November 27, 2007, Dr. Manku "had a discussion recently with Dr. Kono at Mochida"). Mochida marketed a purified EPA product in Japan called Epadel, which was indicated to treat hyperlipidemia and included instructions on the treatment of "an excess of triglycerides." DX 1528 ("Epadel PI 2007") at 1-2, 9. Earlier in 2007, Mochida also published the results of a cardiovascular outcomes study called JELIS, which concluded that "EPA is a promising treatment for prevention of major coronary events." DX 1553 ((Yokoyama et al., Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients (JELIS): a Randomized Open-Label, Blinded Endpoint Analysis, 369 Lancet 1090–98 (2007) ("Yokoyama 2007")) at 1.

235. By at least January 2008, Dr. Manku received "information from Mochida on EPA's effects on LDL" cholesterol, and learned "that Mochida haven't seen any increase in LDL" in patients taking Epadel. DX 1793 at 33-34. Dr. Manku made contact with Mochida's scientists again in April 2008 and reported that it was "quite clear to them that pure EPA does not increase levels of LDL as do EPA+DHA." DX 1856 at 1.

236. Epadel, however, was only sold in Japan. In the United States, the only pharmaceutical fish oil was Lovaza (a/k/a Omacor), which contained both EPA and DHA, and

increased LDL-C. *See* DX 1535 (Lovaza®, Physicians' Desk Reference 2699 (62d ed. 2007) ("Lovaza PDR")) at 2-3. Amarin thus decided to bring a purified EPA product like Epadel to the U.S. market. On May 9, 2008, Amarin sent a letter to FDA formally requesting a meeting to discuss "the preparation and submission of an Investigational New Drug Application for ethyl-EPA in patients with hyperlipidemia." PX 482 (Amarin FDA correspondence) at 1; Ketchum Tr. 73:22-75:7.

b. Plaintiffs' own documents before the alleged March 25, 2008 conception date confirm that the prior art taught all key elements of the asserted claims.

237. Before the alleged March 25, 2008 conception date, Amarin's internal documents confirm that nearly every claim limitation was known based on prior–art teachings. For example, Plaintiffs' internal documents from before March 25, 2008, confirm that the prior art taught Epadel (purified EPA) was approved in Japan to reduce triglycerides, which did not warn about LDL-C increases. DX 1829 at 4-5; Ketchum Tr. 195:1-15; *see also* DX 2241 (showing a March 20, 2008 creation date).

238. Plaintiffs' documents from before March 25, 2008, confirm that the prior art also taught that Lovaza (4 grams/day EPA and DHA) was approved in the United States to treat severe hypertriglyceridemia, and did warn about LDL-C increases. *E.g.*, DX 1814 at 2, 10; Ketchum Tr. 182:23-183:12.

239. Plaintiffs' documents from before March 25, 2008, confirm that Mori studied the differential effects of 4 grams/day 96% pure EPA versus DHA, and found that while both EPA and DHA reduced triglyceride levels, LDL-C increased significantly with DHA and not EPA. *E.g.*, DX 1829 at 7, 11; Ketchum Tr. 199:3-21, 202:23-204:6.

240. And finally, Plaintiffs' documents from before March 25, 2008, confirm that the JELIS study, reported in the prestigious Lancet journal, showed that the frequency of major coronary events is reduced with purified EPA as compared to control. *E.g.*, DX 1814 at 2; Ketchum Tr. 181:21-182:19.

241. Amarin relied on these prior-art studies and teachings because, as of March 2008, Amarin had "not performed any clinical trials of ethyl-EPA in patients with dyslipidemia." DX 1814 at 7.

c. Plaintiffs' evidence does not support a conception date before the filing of its provisional patent application on February 10, 2009.

242. Plaintiffs' evidence does not show that the named inventors conceived of the claimed inventions by March 25, 2008. Instead, Plaintiffs' evidence only shows that one of the named inventors, Dr. Manku, shared publicly-available information with his colleagues.

243. At a March 7, 2008 project team meeting, Dr. Manku was tasked with "ask[ing] Mochida about any publications not translated into English that might be of use." DX 1883 at 1. Shortly thereafter, Dr. Manku circulated three emails to his colleagues, describing EPA's effects and attaching translated publications from Mochida. In their validity contentions and interrogatory answers, Plaintiffs cited these three emails from Dr. Manku in attempt to demonstrate a March 2008 conception date. DX 1953 (Plaintiffs' Validity Contentions) at 16 n.13; ECF No. 292-9 (Ex. 7 to Pls. MIL) (Plaintiffs' Interrogatory answers) at 15-16. Plaintiffs cited their interrogatory answer referencing the same three emails in its motion in *limine*, arguing that the inventors conceived of the claimed inventions by at least March 25, 2008. ECF No. 292 at 6-7.

244. On March 13, 2008, Dr. Manku sent an email to four of his colleagues stating, "[f]urther to our conversation[,] [h]ere are key clinical outcome publications from Mochida on EPADEL," and attached several prior-art studies. DX 1854 at 1. Dr. Manku explained that in these key Mochida publications, "LDL-C is reduced" with Epadel administration. *Id.* On March 16, 2008, Dr. Manku emailed his colleagues another prior-art study from Mochida and relayed that "LDL cholesterol has not been reported to rise after pure EPA." DX 1797 at 1-2. Finally, on March 24, 2008, Dr. Manku explained in another email that "we know from Japanese preclinical and clinical studies EPA does not increase LDL as [does] Omacor." DX 1855 at 1. He recommended "plan[ning] our [clinical] trials so that we can only show similar efficacy to that of Omacor" for reducing triglycerides, but with "careful thought on the secondary outcomes" such as LDL-C. *Id*. at 2.

245. Dr. Manku's March 2008 emails do not show that the inventors conceived of the claimed inventions by March 25, 2008. Dr. Manku's emails are silent about the dose of purified EPA, the duration of treatment, or reducing Apo B.

246. In Plaintiffs' pre-trial findings of fact, Plaintiffs cited two new emails, PX 476 and PX 1132, to support a March 25, 2008 priority date. *See* ECF No. 331 ¶ 24. Defendants had no notice during discovery that Plaintiffs intended to rely on these additional documents as evidence of conception, and therefore had no opportunity to depose the named inventors or Plaintiffs' designated 30(b)(6) witness on conception and reduction to practice, Dr. Juliano, on these documents. Plaintiffs further declined to call Dr. Juliano or any of the named inventors as witnesses at trial.

247. Nevertheless, like the three other emails from Dr. Manku, PX 476 and PX 1132 merely describe publications on EPA by a non-inventor and do not establish a March 25, 2008 priority date. In an email chain from March 24 to 25, 2008, Dr. Manku explained that Dr. Yao, an investigator for a Laxdale-sponsored study for Schizophrenia, "did not notice any increase in LDL" in patients receiving purified 2 g/day of EPA. PX 476 at 1; PX 1132 at 1. These emails do not disclose several of the claimed limitations, including the claimed dose of purified EPA and reducing Apo B.

248. Plaintiffs cannot rely on Dr. Yao's Laxdale-sponsored study in patients with Schizophrenia—or any of Amarin's prior EPA studies—to support an earlier conception date. In a submission to FDA, Amarin made clear that each of its prior studies on Schizophrenia, depression, and Huntington's disease had "major limitations" with regard to lipid data. DX 1816 at 66. On June 16, 2008, Amarin provided FDA with lipid data from Amarin-sponsored studies in its End-of-Phase 2 Meeting Information Package. *Id.* at 1-2, 66. Amarin told FDA that, as of June 2008, it had only conducted CNS studies, none of which "were not designed to recruit and evaluate patients with high triglyceride levels." *Id.* at 66. Patients in its studies further "were not required to be . . . in a fasting state"; therefore, Amarin did not know whether its lipid data "were from fasting or fed state." *Id.* As a result, Amarin explained that its own data showed "[n]o consistent changes in triglyceride and cholesterol levels" across patients treated with EPA. *Id.*

249. Instead, when Amarin began developing Vascepa, it relied entirely on prior-art studies. Despite the "major limitations [with] the efficacy data gathered from Amarin's CNS program

on triglycerides and other lipid parameters," Amarin told FDA that a "large body of evidence supports the efficacy of Ethyl-EPA, administered either as monotherapy or add-on to statin therapy, in reducing triglyceride levels in patients with dyslipidemia of varying severity." *Id.* Amarin further told FDA that such evidence "demonstrate[d] a decrease in triglycerides of approximately 15 to 40%." *Id.*

250. In light of the wealth of prior-art studies on EPA, Amarin did not conduct Phase II trials to gain approval for Vascepa. *See generally id.* A Phase II study is "a proof of concept study before you go into a Phase III registration regulatory study for final indication." Manku Dep. Tr. at 25:10-18. To show proof-of-concept for Vascepa's indication of reducing triglycerides in patients with severe hypertriglyceridemia, Amarin provided FDA with over a dozen prior-art studies "in patients with various levels of hypertriglyceridemia." DX 1816 at 66-67.

251. One of the studies Amarin relied on to show proof-of-concept of treating severely hypertriglyceridemic patients with purified EPA was Mori. In its End-of-Phase 2 Meeting Information Package to FDA, Amarin cited Mori to show EPA's "effects on triglyceride levels." *Id.* Amarin cited Mori again to show that "data suggests that doses between 2 and 4 g/day are likely to produce optimal efficacy." *Id.* at 76-77. And after summarizing the data from Mori and over a dozen other prior-art studies, Amarin concluded that "[i]n clinical studies performed with Ethyl-EPA to date . . . there is no evidence of a significant rise in LDL-cholesterol." *Id.* at 85.

d. Amarin filed its provisional patent application in February 2009 without relying on any clinical data.

252. Upon filing its patent application in February 2009, Amarin still "did not have any data to support the invention at the time these patents were applied for." Manku Dep. Tr. at 79:11-13, 16-19; Osterloh Dep. Tr. at 135:23-136:1, 136:3-13 (agreeing that "when the patent was originally filed we did not have clinical data on the results of the MARINE study"). As a result, the "Examples" section of the patent specifications merely "describe a clinical study" design, but do not "provide the results of the study." Manku Dep. Tr. 76:23-77:3, 77:5-6, 77:8-10; Toth Tr. 1799:14-16 (same). In fact, there is "no animal data or *in vitro* data in the patent" at all. Toth Tr. 1799:17-19.

253. According to Dr. Toth, "even if a skilled artisan came up with a clinical trial protocol that said we're going to use 4 grams pure EPA in patients with triglycerides above 500, and we're hoping that it will be LDL neutral, that would not provide a reasonable expectation of success" in achieving the claimed invention. Toth Tr. 1792:6-12. According to him, "there would not be a reasonable expectation of success until the results come out." *Id.* at 1791:25-1792:5 (Toth). But Amarin did not have access to the MARINE study results until November 2010, long after it filed its patent application. DX 1694 (MARINE Study Report) at 3; Toth Tr. 1793:2-4. Before completing the MARINE study, Amarin had "no clinical trial data in patients with fasting triglyceride levels greater than 500mg/dL" at all. Osterloh Dep. Tr. at 73:11-17. Instead, the named inventors relied on studies in patients with triglycerides below 500 mg/dL to form their reasonable expectation of success. Dr. Bays, the lead investigator for MARINE, testified that he was first contacted about the Vascepa development program by Paresh Soni, one of the named inventors. Bays Dep. Tr. at 34:18-22. According to Dr. Bays, Dr. Soni told him that he believed "there may be a possibility that EPA alone might be able to lower triglyceride levels without increasing LDL cholesterol levels . . . based upon very small studies of patients who did not have very high triglyceride levels." *Id.* at 37:9-20 (Bays).

254. Regardless of whether Plaintiffs are entitled to an earlier priority date, both Dr. Heinecke and Dr. Toth testified that their opinions on obviousness would not change if the priority date were March 2008 or February 2009. Heinecke Tr. 827:8-10; Toth Tr. 1638:5-10.

2. Level of ordinary skill in the art

255. According to Dr. Heinecke, the person of ordinary skill in the art to whom the patents-in-suit are directed would have had (a) at least a medical degree or an advanced degree in the field of lipid biochemistry; (b) several years of experience in the development and/or clinical use of fatty acids to treat blood lipid disorders, including fish oil based fatty acids, *i.e.*, EPA and DHA, and their dosage forms; and (c) access to a team including one or more of a medical doctor, an analytical chemist, or a pharmaceutical chemist. Heinecke Tr. 717:20-718:6.

256. While Dr. Toth offered a slightly different definition on the person of ordinary skill in the art, the differences between Dr. Heinecke and Dr. Toth's definitions do not affect Dr. Heinecke's

opinions. *Id.* at 718:7-13 (Heinecke). Dr. Heinecke was a person of ordinary skill in the art under either definition. *Id.* at 718:14-16 (Heinecke).

3. Scope and content of the prior art

a. Defendants' combination references

i. Lovaza PDR (2007)

257. Lovaza PDR published in 2007 and is prior art to the patents-in-suit.

258. Lovaza PDR discloses a commercially-available preparation of EPA and DHA administered at 4 grams/day. DX 1535 at 2. While the Lovaza PDR published in the 2008 version of the Physician's Desk Reference, Lovaza was first commercially launched in 2004. Heinecke Tr. 745:10-21. Lovaza PDR discloses that "Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (> 500 mg/dl) triglyceride levels." DX 1535 at 3. As of the alleged priority date, Lovaza was "widely used" and "a very successful drug." Toth Tr. 1891:7-12.

259. Lovaza PDR discloses clinical trials in which Lovaza was administered as either "add-on therapy" to a statin or as "monotherapy." DX 1535 at 2. Under "High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy," the label explains:

> The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200-499 mg/dL) despite simvastatin therapy (Table 1).

Id.

260. In this study, Lovaza PDR explains that all patients were treated with "simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C." *Id.* After the addition of Lovaza 4 g per day to simvastatin 40 mg per day, the median change in LDL-C was an increase of 0.7% compared to baseline. *Id.* Relative to placebo, Lovaza 4 g per day further "significantly reduced" TG and Apo-B levels. *Id.* A person of ordinary skill in the art reading Lovaza PDR would understand that "when Lovaza is used with simvastatin, apo B is decreased by 4.2 percent" and

"there's barely any LDL-C increase." Toth Tr. 1872:19-24. In fact, the combination of Lovaza and simvastatin essentially caused "zero" increase in LDL-C. *Id.* at 1872:22-1873:2 (Toth).

261. Lovaza PDR also discloses data under "Very High Triglycerides: Monotherapy" in which "[t]he effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2)." DX 1535 at 2. Table 2 summarizes data from "two studies of 6 and 16 weeks duration." *Id.* In the monotherapy study in patients with very high triglycerides, treatment with Lovaza 4 g/day significantly reduced triglycerides but also caused a significant increase in LDL-C (an increase of 44.5% compared to baseline and 49.3% compared to placebo). *Id.* at 3.

262. Lovaza PDR therefore discloses "Lovaza treatment may result in elevations in LDL-C and non-HDL-C in some individuals." *Id.* However, as of March 2008, a skilled artisan "would understand that if a patient experiences LDL-C increases from Lovaza, [a] statin could be added to address that side effect." Toth Tr. 1891:22-25. A skilled artisan likewise knew that "Lovaza could be safely administered with statins" and was "typically well-tolerated." *Id.* at 1874:22-24, 1893:9-11 (Toth); Heinecke Tr. 810:11-14. In fact, Lovaza's "rise in LDL-C was often offset by concurrent treatment with statins. The safety and efficacy of using prescription Omega-3 in combination with a statin has been well-established." DX 1953 at 233; Toth Tr. 1875:2-16; Heinecke Tr. 809:21-810:10.

ii. Mori (2000)

263. Mori et al., Purified Eicosapentaenoic and Docosahexaenoic Acids Have Differential Effects on Serum Lipids and Lipoproteins, LDL Particle Size, Glucose, and Insulin in Mildly Hyperlipidemic Men, 71 Am. J. Clinical Nutrition 1085–94 (2000) ("Mori") was published in 2000 and is prior art to the patents-in-suit.

264. Mori discloses "a double-blind, placebo-controlled trial of parallel design, 59 overweight, nonsmoking, mildly hyperlipidemic men were randomly assigned to receive 4 g purified EPA, DHA, or olive oil (placebo) daily while continuing their usual diets for 6 wk." DX 1538 at 1-2. The objective of Mori was "to determine whether eicosapentaenoic (EPA) and docosahexaenic (DHA) acids have differential effects on serum lipids and lipoporoteins." *Id.* at 1.

265. Mori discloses that among the three treatment arms, "[c]apsules contained either purified preparations of EPA ethyl ester (~96%), DHA ethyl ester (~92%), or olive oil (~75% oleic acid ethyl ester)." *Id.* at 2. Further, "[n]one of the subjects were regularly taking nonsteroidal antiinflammatory, antihypertensive, or lipid-lowering drugs or other drugs known to affect lipid metabolism." *Id.* at 3. Therefore, none of the patients in Mori were on concurrent lipid-altering therapy. Heinecke Tr. 739:22-25.

266. Mori reports that triacylglycerols (triglycerides) "decreased significantly by 18.4% with EPA (P = 0.012) and by 20% with DHA (*P* = 0.003)." DX 1538 at 3. A person of ordinary skill in the art would consider this difference in triglyceride reduction "indistinguishable and of no clinical significance." Heinecke Tr. 740:1-13. A person of ordinary skill in the art would likewise recognize that Mori teaches that "4 grams pure EPA could reduce triglycerides by about 20 percent." Toth Tr. 1826:24-1827:5.

267. Mori reported that "[s]erum LDL cholesterol increased significantly with DHA (by 8%; P = 0.019), but not with EPA (by 3.5%; NS)," DX 1538 at 3, "strongly suggesting that these two Omega-3 fatty acids could have distinct effects on LDL cholesterol levels." Heinecke Tr. 740:1-17. In the Abstract, Mori summarizes these results as showing that while "LDL, HDL, and HDL_2 cholesterol were not affected significantly by EPA, . . . DHA increased LDL cholesterol by 8% (*P* = 0.019)." DX 1538 at 1; Toth Tr. 1827:8-11. Mori concludes that "EPA and DHA had differential effects on lipids." DX 1538 at 1; Toth Tr. 1827:8-19. Therefore, "a skilled artisan would understand from Mori that DHA and EPA work differently." Toth Tr. 1829:6-8.

iii. Hayashi (1995)

268. Hayashi et al., Decreases in Plasma Lipid Content and Thrombotic Activity by Ethyl Icosapentate Purified from Fish Oils, 56(1) Curr. Therap. Res. 24–31 (1995) ("Hayashi") was published in 1995 and it is prior art to the patents-in-suit.

269. Hayashi reports the daily administration of 1.8 grams per day of purified EPA over a period of eight weeks to patients with a serum triglyceride level above 150 mg/dl. DX 1532 at 4, Hayashi.

270. Hayashi investigated the effects of EPA in patients with "familial combined hyperlipidemia (FCH) showing phenotype Ila, Ilb, or IV." *Id.* While Hayashi defined all three phenotypes as "FCH," *id.*, a person of ordinary skill in the art would have understood that phenotype IV refers to the Fredrickson system of classifying lipid disorders. Toth Tr. 1866:10-12. Fredrickson Type IV is not limited to patients with triglycerides $\geq$ 500 mg/dL. *See, e.g.*, DX 2005 at 6 (reporting a Zocor study in which patients with Fredrickson Type IV had a median triglyceride level of 404 mg/dL). However, this phenotype includes patients with severe hypertriglyceridemia. *See, e.g.*, DX 1986 (current Lipitor label) at 21 (reporting a Lipitor study with a median baseline triglyceride level of 565 mg/dL in patients with Fredrickson Type IV); DX 3007 (2007 Lipitor label) at 11-12; PX 939 (Lovaza statistical review) at 5 (reporting a Lovaza study "in patients with severe hypertriglyceridemia, type IV, with 500 $\leq$ TG $\leq$ 2000 mg/dl").

271. A personal of ordinary skill in the art would have understood that Hayashi includes at least one patient with triglyceride levels $\geq$ 500 mg/dL in light of Hayashi's data. Heinecke Tr. 725:21-727:1. Table I reports that at baseline, the patients in the study had a triglyceride level of 300 ± 233 mg/dl. DX 1532 at 5. Dr. Heinecke explained that while "there is some ambiguity in this paper about what the meaning is of the plus minus 233[,] . . . overwhelmingly, in the medical literature, that would be a standard deviation." Heinecke Tr. 725:21-727:1.

272. The standard deviation is the average spread of the data around the mean value of 300 mg/dl (for a normal distribution of data, two-thirds of the data points are within one standard deviation of the mean). *Id.* (Heinecke). Accordingly, as Dr. Heinecke explained, "[b]ecause there's a value of plus or minus 233, there was at least one patient in that study who had a value of greater than 300, and because that's only encompassing two-thirds of the data, one-sixth of the patients would likely have been above 533." *Id.* (Heinecke). Although Dr. Lavin initially told the PTO that not even one patient in Hayashi would have had triglyceride levels $\geq$ 500 mg/dL, Dr. Lavin later testified that he would "rewrite" his declaration on this point, explaining that in Hayashi "you know that there must be at least one subject" with triglyceride levels $\geq$ 500 mg/dL, and that it is "likely that you have one or two observations above 533." Lavin Dep. Tr. at 102:24-103:21. Dr. Toth did not "offer any type of statistical opinion to corroborate what Dr. Lavin told the patent office." Toth Tr. 1868:13-16.

273. Dr. Heinecke explained that there is an alternative theory that Hayashi's reference to 300 ± 233 mg/dl instead refers to the range of triglyceride values, rather than the standard deviation. Heinecke Tr. 725:21-727:1. But "this would be very unusual," and in any case, under that interpretation there would still be "at least one patient in the study that had a value of 533." *Id.* (Heinecke). Therefore, under either interpretation of Hayashi, at least one patient had triglyceride levels ≥ 500 mg/dL. *Id.* at 727:2-6 (Heinecke).

274. Hayashi discloses that "[a]fter 8 weeks, patients treated with ethyl icosapentate showed significant reductions in . . . triglyceride (41%)," and reports reductions in LDL-C (7%) and apolipoprotein B (7%), which was not statistically significant. DX 1532 at 5. Hayashi therefore concludes that "[p]urified icosapentate (1800 mg/d for 8 weeks) decreased total cholesterol and triglyceride in patients with FCH (Table I)," and that "[n]o overt effects of icosapentate on plasma LDL-C and HDL-C were seen, although a decrease in LDL-C was noted (Table I)." *Id.* at 7.

275. Hayashi does not report the LDL-C data of patients with triglycerides ≥ 400 mg/dL because Hayashi used the Friedewald equation to calculate LDL-C levels. *Id.* at 5; Heinecke Tr. 798:23-800:7. The Friedewald equation is commonly used in clinical studies to calculate LDL-C levels and operates by using triglyceride levels to estimate LDL-C levels, but "is not accurate for triglycerides above 400 milligrams per deciliter." Heinecke Tr. 798:23-800:7. But while Hayashi does not report LDL-C data in patients with triglycerides ≥ 400 mg/dL, Hayashi does not limit its conclusion regarding EPA's effects on LDL-C levels to patients with lower triglyceride levels. Hayashi concludes that "[a]lthough the effects of fish oils on plasma LDL-C and HDL-C are complex, judging from the present study, purified icosapentate apparently has no deleterious effect on plasma LDL-C or HDL-C in patients with FCH." DX 1532 at 5. Again, some patients with FCH—including at least one patient in the Hayashi study—have triglyceride levels above 500 mg/dL. *Id.*; Heinecke Tr. 725:21-727:1; Lavin Dep. Tr. at 102:24-103:21.

276. Hayashi also reports that purified EPA "appear[s] to have an antiatherogenic effect and could be essential in the control of coronary heart disease by lowering plasma lipid content and increasing antithrombotic action." DX 1532 at 3.

iv. Kurabayashi (2000)

277. Kurabayashi et al., Eicosapentaenoic Acid Effect on Hyperlipidemia in Menopausal Japanese Women. Obstet. Gynecol. 96:521–8 (2000) ("Kurabayashi") was published in 2000 and is prior art to the patents-in-suit.

278. Kurabayashi investigated the effects of administering purified EPA (96.5% EPA) at a dose of 1.8 g/day in combination with estriol (the "EPA group") as compared to estriol therapy alone (the "control group") for forty-eight weeks to hyperlipidemic, menopausal women. 1534 at 1. Estriol is a form of estrogen that is commonly used in menopausal women to alleviate the symptoms of menopause. Heinecke Tr. 735:2-20. As an estrogen, estriol is known to elevate triglyceride levels. *Id.* (Heinecke).

279. Despite coadministration with estriol, Kurabayashi reports a statistically significant 27% reduction in triglyceride levels in the EPA group. DX 1534 at 3. As compared to the control group, the EPA group experienced a statistically significant reduction in triglyceride levels at the 12, 24, and 48-week checkpoints:

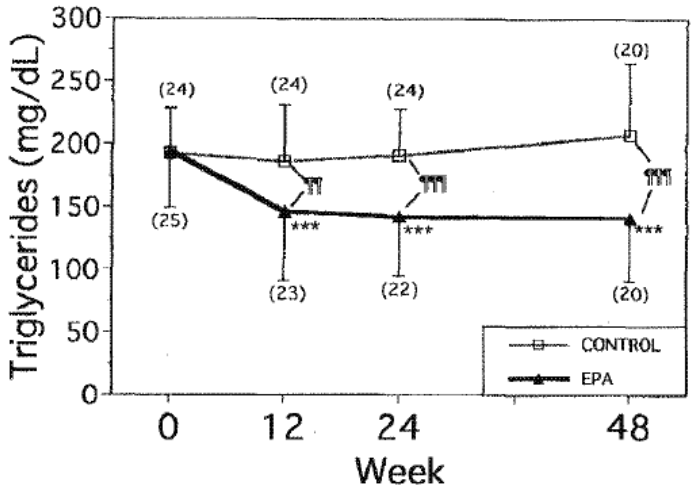

Figure 2. Changes in serum triglycerides levels from baseline to week 48 in the control and eicosapentaenoic acid groups in women whose level of triglycerides was not less than 150 mg/dL at baseline. Abbreviations as in Figure 1. Data are mean ± standard deviation. Numbers in parentheses indicate number of samples. ***$P < .005$ (versus baseline as calculated by Student paired t test). ¶¶$P < .01$. ¶¶¶$P < .005$ (intergroup differences were assessed by Student unpaired t test).

Id. at 5. Kurabayashi further reports that "[l]ow-density lipoprotein cholesterol levels in both groups were significantly lower." *Id.* at 3.

280. Kurabayashi further reports a statistically significant reduction in Apo B levels in the EPA group of 6.9%. *Id.* at 4-5. With a p-value of < .001, EPA's effects on Apo B were highly significant. *Id.*; Heinecke Tr. 737:1-23. In contrast, Kurabayashi reports a non-statistical 1.5% reduction in Apo B levels in the control group:

Table 3. Changes in Serum Levels of Apolipoprotein, Lipoprotein(a), and Remnant Lipoprotein

	Baseline	Week 12	Week 24	Week 48	% change at week 48	P*
n (Control/EPA)	72/69	69/63	66/59	63/55		
Apolipoprotein A-I (mg/dL)						
Control group	153.5 ± 26.3	152.7 ± 27.7	150.0 ± 25.2	150.6 ± 24.1	−1.9	NS
EPA group	152.1 ± 31.6	149.5 ± 28.6	148.2 ± 25.4	150.7 ± 28.5	−0.9	NS
P†	NS	NS	NS	NS		
Apolipoprotein A-II (mg/dL)						
Control group	36.7 ± 4.0	37.5 ± 4.8	36.8 ± 5.2	35.6 ± 5.5	−3.0	NS
EPA group	36.8 ± 6.3	35.3 ± 5.4	34.8 ± 5.3	34.1 ± 5.8	−7.3	.004
P†	NS	.01	.04	NS		
Apolipoprotein B (mg/dL)						
Control group	123.4 ± 18.5	121.9 ± 21.0	121.6 ± 20.1	121.5 ± 18.6	−1.5	NS
EPA group	124.8 ± 18.7	119.4 ± 21.5	119.3 ± 20.4	116.2 ± 19.3	−6.9	< .001
P†	NS	NS	NS	NS		

DX 1534 at 4-5; Heinecke Tr. 737:1-23.

281. The results reported in Kurabayashi do not suggest any interaction or synergy between EPA and estriol. Heinecke Tr. 735:21-736:9. Instead, synergy is usually only seen between drugs that have similar effects, such as two drugs that reduce blood pressure. *Id.* (Heinecke).

282. In light of the statistically-significant differential effects reported between the EPA and control groups, a person of ordinary skill in the art would have attributed the reduction in Apo B to EPA. *Id.* at 737:24-738:8 (Heinecke).

b. Background and state of the art

i. Triglyceride-lowering therapies focused on patients with triglycerides ≥ 500 mg/dL.

283. In 2001, the National Cholesterol Education Program published an executive summary of its ATP III Guidelines, which provided "updated clinical guidelines for cholesterol testing and management" and "expands the indications for intensive cholesterol-lowering therapy in clinical practice." DX 1526 (ATP-III Executive Summary) at 10.

284. ATP III identifies LDL-C as the primary target of cholesterol-lowering therapy. ATP III explains that "recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD [coronary heart disease]. For these reasons, ATP-III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL." *Id.* at 11. Accordingly, ATP III explains that "[f]or all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol." *Id.* at 27.

285. However, ATP III outlined a different treatment approach for patients with severely elevated triglycerides. ATP III explains that "[i]n rare cases in which triglycerides are very high (≥500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. *Id.* at 28. In these patients, "[o]nly after triglyceride levels have been lowered to <500 mg/dL should attention turn to LDL lowering to reduce risk for CHD." *Id.* at 28. ATP III assigned these different treatment priorities to patients above or below 500 mg/dL because "above 500, doctors should be primarily concerned about pancreatitis risk." Toth Tr. 1859:3-13; Bays Dep. Tr. at 143:9-11, 143:13-19 ("[T]he purpose of the 500 mg/dL cutoff point is to assign the priority of treatment . . . to reduce the risk of pancreatitis."). "The 500 threshold was not set because above 500 you are expected to have a greater increase in LDL-C" in response to triglyceride-lowering medications. Toth Tr. 1860:4-7.

286. In the late 1990s and 2000s, FDA approved several medications to reduce triglycerides in patients with elevated triglyceride levels. For example, FDA approved Tricor "as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia)." DX 1598 at 7; *see also id.* at 8 (explaining that patients with Fredrickson Types IV and V have "major" triglyceride elevations).

287. FDA also approved Lipitor "as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV)." DX 1986 (current Lipitor label) at 2; *see also* DX 3007 (2007 Lipitor label) at 14. The Lipitor study supporting approval for this indication reports a median baseline triglyceride level of 565 mg/dL. DX 1986 (current Lipitor label) at 21; *see also*

DX 3007 (2007 Lipitor label) at 11-12. The Lipitor label therefore describes treating some patients with severe hypertriglyceridemia. Toth Tr. 1815:6-18.

288. In 2004, consistent with ATP III, FDA approved Lovaza "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (> 500 mg/dl) triglyceride levels." DX 1535 (Lovaza PDR) at 3.

289. Despite ATP III's focus on the cutpoint of triglycerides ≥ 500 mg/dL, the FDA-approved labeling for each of the above triglyceride-lowering medications reported data in patients with triglycerides < 500 mg/dL. For example, although Lovaza was approved solely to reduce triglycerides in patients with severe hypertriglyceridemia, the Clinical Studies section of the label reports data from a clinical trial in patients with triglycerides between 200 and 499 mg/dL. DX 1535 (Lovaza PDR) at 2. As Dr. Peck explained, FDA only includes in the Clinical Studies section "those clinical studies that facilitate an understanding of how to use the drug safely and effectively." Peck Tr. 1332:23-1333:7. Here, FDA determined that Lovaza's triglyceride-lowering effects in patients with triglycerides between 200 and 499 mg/dL would have facilitated a doctor's understanding of how to use Lovaza safely and effectively in patients with triglycerides ≥ 500 mg/dL. DX 1535 (Lovaza PDR) at 2.

290. Similarly, to support its indication in patients with Fredrickson Types IV and V, the Tricor label includes data in patients with baseline triglyceride levels between 350 and 499 mg/dL. DX 1598 at 7. The Lipitor label likewise reports data in patients with baseline triglyceride levels below 500 mg/dL—ranging from 267 to 1502 mg/dL. DX 1986 (current Lipitor label) at 21; *see also* DX 3007 (2007 Lipitor label) at 11-12.

ii. Purified EPA was known and commercially available.

291. A highly purified EPA formulation, Epadel, was commercially available and approved in Japan in the early 1990s. DX 1527 (Epadel Capsules 300, Japan Pharmaceutical Reference 369 (2nd ed. 1991) ("Epadel label")) at 3-4. Thus, as of March 2008, "a skilled artisan would have been aware of Epadel, at a minimum, because of the JELIS trial." Toth Tr. 1823:12-14.

292. By 2000, Epadel contained "over 96.5% eicosapentaenoic acid ethyl ester." DX 1534 (Kurabayashi) at 2. By 2003, Epadel was formulated to contain 98% EPA. DX 1552 (Yokoyama et

al., Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS), 146 Am. Heart J. 613–20 (2003) ("Yokoyama 2003")) at 3. Mochida's JELIS study likewise reported that Epadel contained 98% pure EPA. DX 1553 (Yokoyama 2007) at 2. At a minimum, by 2007 Mochida continued to formulate Epadel as containing a "proportion of EPA-E in total fatty acid [of] at least 96.5%." DX 1524 (WO 2007/142118 ("WO '118")) at 25.

293. Numerous other forms of highly purified EPA, and processes to make them, were known in the prior art. For example, WO '118 generally taught that "the EPA-E used is preferably the one having a high purity, . . . more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher." DX 1524 at 25. Mori also disclosed EPA preparations that are ~96% pure. DX 1538 at 2.

294. WO 2008/004900 ("WO '900") taught highly-purified compositions of EPA, which are free of undesired molecules such as DHA and arachidonic acid. DX 1525 at 2. WO '900 teaches that "the desired effects of EPA are limited or even reversed by the co-consumption of undesired molecules; (as herein defined) in particular docosohexaenoic acid (DHA); . . . and other omega-3 and 6 fatty acids in general." *Id.* at 6. WO '900 therefore teaches that "to enable effective pharmaceutical or therapeutic use of EPA, high purity dosage forms, free of the undesired molecules, are required." *Id.* Consistent with this teaching, WO '900 taught a composition that "comprises between 99.6 and 99.9% EPA" and "less than 0.1% of DHA." *Id.* at 17. WO '900 further described in detail processes for achieving highly-purified EPA-rich compositions, and provided examples regarding production of highly-purified EPA compositions. *Id.* at 24-31.

iii. Purified EPA was known to reduce triglycerides.

295. As early as 1991, Epadel was studied for its usefulness "in the treatment of hyperlipidemia," which would include patients with hypertriglyceridemia. DX 1550 (Takaku et al., *Study on the Efficacy and Safety of Ethyl Icosapentate (MND-21) in Treatment of Hyperlipidemia Based on a Long-Term Administration Test*, 7 J. Clin. Therapeutics & Medicine 191–213 (1991) ("Takaku")) at 4; Heinecke Tr. 720:1-13. The Takaku study reported that in patients treated with Epadel, "the rate of decrease in the serum triglyceride is approximately 20%." DX 1550 at 32. By

1998, Mochida published an article reporting the results of Epadel for use in hyperlipidemia. DX 1546 (Saito et al., *Results of Clinical Usage of Improved Formulation (MND-21S) Epadel Capsule 300 with Respect to Hyperlipidemia*, 26(12) Jpn. Pharmacol. Ther. 2047–62 (1998) ("Saito 1998")) at 1.

296. By at least 2003, Epadel was indicated to treat hyperlipidemia. Heinecke Tr. 743:23-744:3. Epadel PI 2007 likewise states that it is indicated to treat hyperlipidemia, and specifies that "when an excess of triglycerides are presented . . . the dosage may be increased. DX 1528 at 1-2.

297. Mori likewise taught that 4 g/day of 96% purified EPA reduced triglycerides by 18.4%. DX 1538 at 2-3. A person of ordinary skill in the art would therefore recognize that Mori teaches that "4 grams pure EPA could reduce triglycerides by about 20 percent." Toth Tr. 1826:24-1827:5.

298. Numerous other prior-art studies reported that purified EPA reduced triglycerides by substantial amounts. Toth Tr. 1855:20-25; *see also, e.g.*, DX 1551 (Wojenski et al., Eicosapentaenoic Acid Ethyl Ester as an Antithrombotic Agent: Comparison to an Extract of Fish Oil, Biochim. Biophys. Acta., 1081(1):33–38 (1991)) ("Wojenski") at 2, 4 (reducing triglycerides by 33%); DX 1532 (Hayashi) at 5 (reducing triglycerides by 41%); DX 1534 (Kurabayashi) at 3 (reducing triglycerides by 27%); DX 1530 (Grimsgaard et al., Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid in Humans Have Similar Triacylglycerol-Lowering Effects but Divergent Effects on Serum Fatty Acids, 66 Am. J. Clin. Nutr. 649–59 (1997) ("Grimsgaard 1997")) at 2 (reducing triglycerides by 21%); DX 1541 (Nozaki et al., Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary Hypercholesterolemia, 62 Int'l J. Vitamin & Nutrition Res. 256–60 (1992) ("Nozaki 1992")) at 4-5 (reducing triglycerides by 16%).

iv. Combination DHA/EPA products were known to increase LDL-C.

299. In 1997, an article authored by Harris disclosed a combination EPA/DHA product that was under investigation, which later became Lovaza. DX 1531 (Harris et al., *Safety and Efficacy of Omacor in Severe Hypertriglyceridemia*, J. Cardiov. Risk, 4:385–391 (1997) ("Harris")) at 1;

Heinecke Tr. 730:13-731:7. Harris taught that 4 g/day of EPA and DHA undesirably increased LDL-C by 31%. DX 1531 at 1; Heinecke Tr. 732:2-9.

300. The Lovaza PDR reports an even higher increase in LDL-C levels with EPA/DHA 4 g/day monotherapy: an increase of 44.5% compared to baseline and 49.3% compared to placebo. DX 1535 at 3. As of March 2008, "the LDL-C increases with Lovaza was an important problem warranting new solutions." Toth Tr. 1786:17-19. Therefore, "a skilled artisan would have been motivated to avoid LDL-C increases when treating patients with severe hypertriglyceridemia." *Id.* at 1822:8-11 (Toth). A skilled artisan further "would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases." *Id.* at 1822:18-21 (Toth).

v. Unlike DHA, EPA did not increase LDL-C.

301. By the early 1990s, it was "suggested that EPA and DHA have different properties against lipoprotein metabolism." DX 1541 (Nozaki 1992) at 3. Nozaki therefore "investigated the effects of purified eicosapentaenoic acid (EPA) . . . on plasma lipoproteins." *Id.* Nozaki reported that "low density lipoprotein (LDL)-C levels were significantly reduced" with EPA administration, *id.*, teaching that EPA administration could reduce triglyceride levels without increasing LDL-C. Heinecke Tr. 724:19-725:9.

302. Grimsgaard 1997 conducted "a double-blind, placebo-controlled, parallel design intervention study" in 234 patients to compare the effects of 3.8 g/day of EPA and DHA on serum lipids and apolipoproteins. DX 1530 at 1. Each arm of the study included approximately 70 to 75 patients. *Id.* at 5. In the EPA arm, purified EPA reduced LDL-C by 8%. *Id.* In contrast, in the DHA arm, purified DHA increased LDL-C by 7%. *Id.* Neither result was statistically significant. *Id.* Nonetheless, Grimsgaard 1997 concluded that "both DHA and EPA lower serum triacylglycerol concentration, but have differential effects on lipoprotein and fatty acid metabolism in humans." *Id.* at 9. In light of Grimsgaard 1997, a person of ordinary skill in the art would have understood that "purified EPA would not increase LDL cholesterol, and may, in fact, decrease[] it, although that change was not significant." Heinecke Tr. 729:20-730:3.

303. Mori subsequently conducted "a double-blind, placebo-controlled trial of parallel design, 59 overweight, nonsmoking, mildly hyperlipidemic men were randomly assigned to receive

4 g purified EPA, DHA, or olive oil (placebo) daily while continuing their usual diets for 6 wk." DX 1538 at 1-2. The objective of Mori was "to determine whether eicosapentaenoic (EPA) and docosahexaenic (DHA) acids have differential effects on serum lipids and lipoporoteins." *Id.*

304. Mori reported that "[s]erum LDL cholesterol increased significantly with DHA (by 8%; P = 0.019), but not with EPA (by 3.5%; NS)," DX 1538 at 3, "strongly suggesting that these two Omega-3 fatty acids could have distinct effects on LDL cholesterol levels." Heinecke Tr. 740:1-17. While Mori reports a small increase in LDL-C in the EPA group, a person of ordinary skill in the art would not interpret this to mean that EPA increases LDL-C because the result was not statistically significant. *Id.* at 740:18-25 (Heinecke). The purpose of attributing statistical significance to a study result is to determine whether or not the result is due to chance. *Id.* (Heinecke). If a drug is LDL-neutral and "one repeatedly measures a variable over and over again, . . . by chance alone you can have a small increase or decrease." *Id.* (Heinecke). At a minimum, in light of Mori a skilled artisan would "believe that a future study assessing differential results on LDL-C, between purified EPA and DHA, would be warranted." Toth Tr. 1829:25-1830:6. And overall, Mori would have taught a skilled artisan "that DHA and EPA work differently." *Id.* at 1829:6-8 (Toth).

305. Numerous other references taught or suggested that EPA was LDL-C-neutral. Takaku reported that "[i]n terms of the rate of change in serum LDL-cholesterol, no significant fluctuation was observed throughout the entire period" of receiving Epadel. DX 1550 at 21; Heinecke Tr. 721:24-722:4. Hayashi taught that EPA administration "had no statistical significant effect on LDL-C," concluding that in light of "the present study, purified icosapentate apparently has no deleterious effect on plasma LDL-C." DX 1532 at 5, 7. In JELIS, the authors echoed that "EPA did not affect LDL cholesterol concentrations" upon administering purified EPA with a statin as compared to statin therapy alone. DX 1553 (Yokoyama 2007) at 7; *see also* DX 1534 (Kurabayashi) at 3 (reporting that upon assessing the addition of EPA to estriol as compared to estriol alone, "[l]ow-density lipoprotein cholesterol levels in both groups were significantly lower"). And unlike the Lovaza label, the Epadel label did not include a warning about LDL-C increases. DX 1528 at 1-2; Heinecke Tr. 748:6-8.

306. In contrast, it was known that "[m]ost . . . studies of DHA supplementation have shown increases in LDL cholesterol . . . ranging from -2.8% to 16.0% (median = 7.2%)." DX 1536 (Maki et al., *Lipid responses to a dietary docosahexaenoic acid supplement in men and women with below average levels of high density lipoprotein cholesterol*, 24 J. Am. Col. Nutr. 189–99 (2005) ("Maki")) at 1, 9. Maki would have provided a person of ordinary skill in the art with "very strong evidence that DHA, one of the two components of Lovaza, or highly-purified fish oil, is very likely responsible for the increase in LDL cholesterol levels." Heinecke Tr. 744:10-745:4.

307. Plaintiffs rely on two other references as evidence that DHA sometimes did not increase LDL-C. *See* DX 1933 (Agren et al., *Fish Diet, Fish Oil and Docosahexaenoic Acid Rich Oil Lower Fasting and Postprandial Plasma Lipid Levels*, 50 European J. Clinical Nutrition 765, 770 (1996) ("Agren")) at 4, 6; DX 1949 (Conquer et al., *Supplementation with an Algae Source of Docosahexaenoic Acid Increases (n-3) Fatty Acid Status and Alters Selected Risk Factors for Heart Disease in Vegetarian Subjects*, 126 J. Nutrition 3032 (1996) ("Conquer")) at 1. But neither reference compared EPA to DHA. Rather, both references tested DHA alone. Heinecke Tr. 779:20-21, 780:13-16. Moreover, Agren did not "draw any definite conclusion about whether DHA increases LDL-C." Heinecke Tr. 779:17-19. In fact, Agren made clear that "the *only* definite conclusion which can be made on the basis of this study is that [ ] DHA is effective in lowering fasting plasma triglyceride concentrations." DX 1933 at 6 (emphasis added). Both Conquer and Agren also published before Mori reported the differential effects between EPA and DHA. *See* DX 1933 (Agren) at 1; DX 1949 (Conquer) at 1. As such, a person of ordinary skill in the art would not have looked to Agren or Conquer to compare the effects of EPA with DHA. Heinecke Tr. 779:17-780:22.

308. Plaintiffs rely on Rambjør, which reported that EPA "produced significant decreases in both TG and very low density lipoprotein (VLDL) cholesterol," but was also associated with a statistically significant "increase[] in low density lipoprotein cholesterol levels." DX 1961 (Rambjør et al., *Eicosapentaenoic Acid Is Primarily Responsible for Hypotriglyceridemic Effect of Fish Oil in Humans*, 31 Lipids S-45 (1996) ("Rambjor")) at 3. But Rambjør used only 3 g/day of EPA that was only 91% pure. DX 1961 at 1, 3. Because "omega-3s are complex," Dr. Toth testified that a skilled

artisan "would have no idea" what fatty acids are in the other 9%, which could have included a substantial amount of DHA. Toth Tr. 1814:17-22.

309. Rambjør also consolidated data from three separate studies and only included 9 patients in the DHA group. *Id.* Rambjør further only included a 2-week washout period, and patients were only given EPA or DHA for a period of 3 weeks. *Id.* The Rambjør study was therefore underpowered, and its design of comparing the effects of two drugs with a significantly different number of subjects in each group was unusual. Heinecke Tr. 782:4-783:1. Rambjør itself concluded that "[f]urther studies are needed to clearly define individual effects of EPA and DHA on human lipid metabolism." DX 1961 at 6.

310. Mori is "one of those further studies" that clearly defined the individual effects of EPA and DHA on human lipid metabolism. Toth Tr. 1842:10-17. Mori, which published after Rambjør, criticized Rambjor's design as studying "only a small number of subjects in the DHA group," for being of "short duration," and for including "only a 2-wk washout period between treatments." DX 1538 at 5, 9. In contrast to Mori—which studied the claimed EPA dose and purity (4/g day at 96% purity), DX 1538 at 2—the EPA studied in Rambjør was only 91% pure and administered at only 3 g/day. DX 1961 at 3; Toth Tr. 1841:7-1842:1. A person of ordinary skill in the art as of March 2008 thus would have relied on the teachings of Mori over those in the earlier Rambjør reference—particularly if the skilled artisan were focusing on a dose of 4 g/day and at least 96% purity, as used in Mori but not in Rambjør. Heinecke Tr. 784:22-785:2. This is evidenced by the fact that Mori has been repeatedly cited in the literature, including Amarin internal documents and submissions to the FDA, but Plaintiffs have not identified any trial exhibit that cites Rambjør other than von Schacky, discussed below. *See, e.g.*, DX 1816 at 68 (Amarin summarizing over a dozen prior-art EPA studies to FDA, including Mori but not Rambjør); DX 1800 at 12-13 (Amarin summarizing DHA and EPA's effects on LDL-C in an investor presentation and citing Mori but not Rambjør).

311. Another reference relied on by Plaintiffs, von Schacky, did not report any primary data on EPA or DHA's effects, but reported in a table that studies suggested that both EPA and DHA increase LDL-C. DX 1605 (von Schacky, *A review of omega-3 ethyl esters for cardiovascular prevention and treatment of increased blood triglyceride levels*, Vascular Health and Risk

Management 2(3):251-262 (2006) ("von Schacky")) at 9; Toth Tr. 1844:9-14. The table, however, merely included arrows pointing in different directions and did not attribute any significance to any of the variables reported. DX 1605 at 9; Heinecke Tr. 785:23-786:22.

312. Von Schacky further reported inconsistent information, citing Mori and claiming that "[i]n more recent comparative studies, no effects of either EPA or DHA . . . were seen on LDL levels." DX 1605 at 5. As Dr. Toth conceded, "[t]hat's not what Mori said." Toth Tr. 1847:8-17. Mori expressly reported that "[s]erum LDL cholesterol increased significantly with DHA (by 8%; P = 0.019)." DX 1538 at 1. Because von Schacky is a review article, a skilled artisan further would have looked at the underlying clinical studies cited by von Schacky, including Mori. Toth Tr. 1848:4-8.

313. In any event, as Dr. Heinecke explained, because EPA is LDL-neutral, one would expect to see small increases or decreases across studies due to chance alone. Heinecke Tr. 740:18-25. Therefore, if among the available literature on EPA's effects on LDL-C you saw "one-third of the studies showing an increase, one-third of the stud[ies] showing a decrease, and one third of the stud[ies] showing no effect, that would be very strong evidence that there was no overall effect on the intervention." *Id.* 781:21-782:3 (Heinecke).

vi. A skilled artisan would not have extrapolated the LDL-C effects of other compounds on EPA.

314. In light of the state of the art, a person of ordinary skill in the art would not have assumed that EPA would increase LDL-C levels in patients with severe hypertriglyceridemia. Heinecke Tr. 800:8-21, 859:8-860:4.

315. For example, while fibrates were known to cause different effects on LDL-C levels in different patient populations, this was not the "general rule for lipid therapies" and has "no significance . . . [on] other agents that are completely structurally and functionally unrelated to fibric acid derivatives. *Id.* at 910:21-911:3 (Heinecke). Fibrates and omega-3 fatty acids are structurally very different, and the prior art did not suggest that they operate by similar mechanisms. *Id.* at 801:12-23 (Heinecke).

316. During prosecution, the examiner likewise found that because "Triplix [sic] (fenofibric acid is structurally and biologically very different from EPA-E . . . one cannot extrapolate

the results observed with a fibrate (Triplix [sic]) to omega-3-fatty acids like EPA-E." DX 1587 at 19. The effects of fibrates on LDL-C levels therefore "cannot be predictive of a similar behavior (dramatic LDL increase in the very high TG group)" upon administration of EPA in the same patient population. *Id.* In light of these differences, a person of ordinary skill in the art as of March 2008 would not have assumed that fibrates and EPA have the same mechanism of action. Heinecke Tr. 802:4-7.

317. Plaintiffs cite a 1977 article by Carlson to argue that a skilled artisan would have expected niacin to increase LDL-C levels in patients with severe hypertriglyceridemia. *See* PX 1026 (Carlson et al., *On the rise in low density and high density lipoproteins in response to the treatment of hypertriglyceridaemia in type IV and type V hyperlipoproteinaemias*, 26 Atherosclerosis 603 (1977) ("Carlson")). While Carlson referenced LDL-C increases in patients administered niacin with severe hypertriglyceridemia, PX 1026 at 3, Carlson only involved nine patients—only five of whom were administered niacin—and did not report any triglyceride data. Heinecke Tr. 855:21-856:12, 912:9-12. Furthermore, "there is not any structural similarity between niacin and EPA." *Id.* at 911:19-912:4 (Heinecke). Carlson therefore would not have "told a person of skill in the art anything about whether EPA would increase LDL-C in patients with severe hypertriglyceridemia." *Id.* at 912:13-17 (Heinecke).

318. Likewise, while Lovaza PDR taught that a combination of DHA and EPA increased LDL-C levels in patients with severe hypertriglyceridemia, DX 1535 at 3, "a skilled artisan would understand from Mori that DHA and EPA work differently." Toth Tr. 1829:6-8. And "the fact that Lovaza itself has an LDL-C side effect doesn't answer the question of whether that side effect could be attributed to solely EPA or solely DHA." *Id.* at 1801:21-25 (Toth). A skilled artisan therefore would understand that "it could be EPA that was a problem, it could be DHA that was a problem, [or] it could be both that was a problem," but a skilled artisan would not have assumed that both EPA and DHA necessarily caused the increase in LDL-C levels. Heinecke Tr. 760:16-761:5.

319. At most, Plaintiffs' evidence on the LDL-C effects in patients with severe hypertriglyceridemia showed differential increases in LDL-C levels in patients with triglyceride levels well above 500 mg/dL. But "every asserted claim in this case covers patients with triglyceride

levels of 500 and above," therefore each claim "includes patients who have a triglyceride level of only 500." Toth Tr. 1818:24-1819:1.

320. For example, Lovaza PDR showed significant increases in LDL-C in patients with a median baseline triglyceride level of 816 mg/dL. DX 1535 at 3. But Dr. Toth testified that, as of March 2008, "a skilled artisan would expect different LDL-C effects from a drug treating a patient with a baseline triglyceride level of 500, as opposed to a patient with a triglyceride level above 800." Toth Tr. 1818:15-19. This is because it was known that "the higher the triglyceride baseline, the more likely you are to have an LDL-C increase." *Id.* at 1818:8-11 (Toth).

321. With respect to Tricor, Plaintiffs' evidence shows that in patients administered Tricor with a mean triglyceride level of 432 mg/dL, PDX 6-7, "there was no statistically significant increase in LDL-C." Toth Tr. 1819:22-1820:14. The Tricor study further included patients with triglyceride levels up to 499 mg/dL, PDX 6-7, and "triglyceride levels of 499 and 500 are within error of the measurement." Toth Tr. 1820:15-17. While significant increases in LDL-C were observed in patients with a mean triglyceride level of 726, PDX 6-7, there is "no claim in this case that requires triglycerides above 700." Toth Tr. 1820:23-1821:2.

322. Plaintiffs' theory also ignored medications approved by FDA to treat severely hypertriglyceridemic patients that were not associated with LDL-C increases. Heinecke Tr. 853:4-10. Specifically, statins, also called HMG-CoA reductase inhibitors, were known to reduce triglycerides without increasing LDL-C in patients with severe hypertriglyceridemia. *Id.* (Heinecke). The Lipitor label reports a study with patients having a median baseline triglyceride level of 565 mg/dL, and upon administration with a 20 mg dose, triglycerides decreased by 38.7% and LDL-C decreased by 30.4%. DX 1986 (current Lipitor label) at 21; *see also* DX 3007 (2007 Lipitor label) at 11-12. Substantial reductions in both triglycerides and LDL-C were likewise seen with both the 10 mg and 80 mg strengths. *Id.* (reporting a 41% reduction in triglycerides and 26.5% reduction in LDL-C, and a 51.8% reduction in triglycerides and 40.5% reduction in LDL-C, respectively). The Lipitor label therefore describes achieving reductions in both triglycerides and LDL-C levels in patients with severe hypertriglyceridemia. *Id.*; Toth Tr. 1815:6-18.

323. While EPA's mechanism of action was not entirely understood, some literature further suggested that EPA may function in part by the same mechanism as statins. *See* Heinecke Tr. 858:16-859:7. An article sponsored by Mochida explains that animal studies suggested that EPA might suppress "cholesterol biosynthesis in the liver" due to a decrease in "the HMG-CoA reductase activity of hepatic microsomes." DX 1797 (Mizuguchi et al., *Hypolipidemic Effect of Ethyl all-cis-5,8,11,14,17-Icosapentaenoate (EPA-E) in Rats*, 59 Japan J. Pharmacol. 307-312 (1992) ("Mizuguchi")) at 6.

vii. A skilled artisan would have known that purified EPA reduces Apo B.

324. Kurabayashi reported that upon administering purified EPA (96.5% EPA) with estriol (the "EPA group") as compared to estriol therapy alone (the "control group"), the EPA group resulted in a statistically significant reduction in Apo B levels of 6.9%. DX 1534 at 1, 4-5. With a p-value of < .001, EPA's effects on Apo B were highly significant. *Id.*; Heinecke Tr. 737:1-23. In contrast, Kurabayashi reports a non-statistical 1.5% reduction in Apo B levels in the control group:

Table 3. Changes in Serum Levels of Apolipoprotein, Lipoprotein(a), and Remnant Lipoprotein

	Baseline	Week 12	Week 24	Week 48	% change at week 48	P*
n (Control/EPA)	72/69	69/63	66/59	63/55		
Apolipoprotein A-I (mg/dL)						
Control group	153.5 ± 26.3	152.7 ± 27.7	150.0 ± 25.2	150.6 ± 24.1	−1.9	NS
EPA group	152.1 ± 31.6	149.5 ± 28.6	148.2 ± 25.4	150.7 ± 28.5	−0.9	NS
p†	NS	NS	NS	NS		
Apolipoprotein A-II (mg/dL)						
Control group	36.7 ± 4.0	37.5 ± 4.8	36.8 ± 5.2	35.6 ± 5.5	−3.0	NS
EPA group	36.8 ± 6.3	35.3 ± 5.4	34.8 ± 5.3	34.1 ± 5.8	−7.3	.004
p†	NS	.01	.04	NS		
Apolipoprotein B (mg/dL)						
Control group	123.4 ± 18.5	121.9 ± 21.0	121.6 ± 20.1	121.5 ± 18.6	−1.5	NS
EPA group	124.8 ± 18.7	119.4 ± 21.5	119.3 ± 20.4	116.2 ± 19.3	−6.9	< .001
p†	NS	NS	NS	NS		

DX 1534 at 4-5.

325. Dr. Toth testified that a skilled artisan reading Kurabayashi would not "have drawn any conclusions about the lipid effects of EPA alone" because "there was no mono[]therapy arm of the study." Toth Tr. 1663:9-13. But given that Kurabayashi included an estriol-only "control" group, DX 1534 at 1, an EPA monotherapy group would only be necessary if EPA and estriol exhibited synergy in reducing Apo B.

326. The results reported in Kurabayashi do not suggest any interaction or synergy between EPA and estriol. Heinecke Tr. 735:21-736:9; *id.* at 735:2-20 (Heinecke). Synergy is usually only seen between drugs that have similar effects, such as two drugs that reduce blood pressure, and estriol is a form of estrogen that (unlike EPA) is known to elevate triglyceride levels. *Id.* at 735:2-736:9 (Heinecke). In light of the statistically-significant differential effects reported between the EPA and control groups, a person of ordinary skill in the art would have attributed the reduction in Apo B to EPA. *Id.* at 737:24-738:8 (Heinecke).

327. Additional references disclosing administration of EPA-only supported Kurabayashi's findings. *Id.* at 737:24-738:9-25 (Heinecke). Nozaki 1992 reported that "apolipoprotein (apo) B100 levels were significantly reduced" with EPA administration, DX 1541 a3-4, teaching that "purified EPA could reduce apo B levels." Heinecke Tr. 725:7-9. In Grimsgaard 1997, administration of 3.8 g/day of purified EPA reduced Apo B by 3%, which achieved statistical significance. DX 1530 a1, 5; Heinecke Tr. 729:5-17. In light of Grimsgaard 1997, a person of ordinary skill in the art would understand that purified EPA "could induce a significant 3 percent reduction in apo B levels." Heinecke Tr. 729:20-730:3.

328. Taken together, Kurabayashi, Nozaki, and Grimsgaard 1997 provide "very strong evidence that apo B levels can in fact be lowered by EPA therapy." *Id.* at 738:20-25 (Heinecke).

viii. A skilled artisan would have known that EPA was safely administered with statins, which reduced triglycerides, LDL-C, and Apo B.

329. It is undisputed that "seven of the ten claims asserted in this case allow for use of a statin with icosapent." Toth Tr. 1886:11-14. These seven claims[6] contain the open-ended term "comprising" and, unlike the three other asserted claims,[7] cover methods of treatment that include using "a concurrent lipid-altering therapy." These seven claims therefore allow addition of a statin to the claimed method to avoid an LDL-C increase, or to reduce Apo B. *Id.*; Toth Tr. 1886:15-24.

[6] Claim 1 and 8 of the '677 patent (DX 1504); claim 1 of the '652 patent (DX 1506); claim 4 and 17 of the '560 patent (DX 1514); claim 1 and 5 of the '929 patent (DX 1516).

[7] Claim 1 and 16 of the '728 patent (DX 1500); claim 14 of the '715 patent (DX 1502).

330. As of March 2008, it was well known that omega-3 fatty acids, including EPA, could be safely administered with statins to reduce triglycerides, LDL-C, and Apo B. For example, Lovaza PDR discloses a clinical trial in which Lovaza (EPA and DHA) was administered as "add-on therapy" to a statin, in which patients were treated with "simvastatin 40 mg . . . to control their LDL-C." DX 1535 at 2. Zocor (simvastatin), like other HMG-coA reductase inhibitors, was specifically indicated at the time to "[r]educe elevated total-C, LDL-C, Apo-B and TG." DX 2005 (Zocor label) at 1, 8.

331. Lovaza PDR reports, after administering both Lovaza 4 g and simvastatin 40 mg per day, a median LDL-C increase of only 0.7% compared to baseline in patients with high triglycerides, which was not statistically significant. DX 1535 at 2. Relative to placebo, the administration of Lovaza 4 g per day and a statin further "significantly reduced" TG and Apo-B levels. *Id.* A person of ordinary skill in the art reading Lovaza PDR would understand that "when Lovaza is used with simvastatin, apo B is decreased by 4.2 percent" and "there's barely any LDL-C increase." Toth Tr. 1872:19-24. In fact, the combination of Lovaza and simvastatin essentially caused "zero" increase in LDL-C. *Id.* at 1872:22-1873:2 (Toth).

332. As of March 2008, a skilled artisan "would understand that if a patient is experiencing LDL-C increases because of Lovaza, a statin could be added." *Id.* at 1874:16-18 (Toth). A skilled artisan likewise knew that "Lovaza could be safely administered with statins" and was "typically well-tolerated." *Id.* at 1874:22-24, 1893:9-11 (Toth); Heinecke Tr. 810:11-14. In fact, Lovaza's "rise in LDL-C was often offset by concurrent treatment with statins. The safety and efficacy of using prescription Omega-3 in combination with a statin has been well-established." DX 1953 at 233; Toth Tr. 1875:2-16; Heinecke Tr. 809:21-810:10.

333. In diabetic patients with severe hypertriglyceridemia, statin therapy was the standard of care as of March 2008, regardless of the patients' LDL-cholesterol levels. Fisher Tr. 958:4-8; *see also* Toth Tr. 1897:8-10. "[W]hen a patient is on a moderate-intensity statin or high-intensity statin, the increase in LDL cholesterol is not a concern because the statin is lowering the levels of LDL cholesterol because of the way statins work." Fisher Tr. 958:9-12 (Fisher).

334. By March 2008, a skilled artisan also "would be very familiar with the LIPITOR label," another statin medication. Toth Tr. 1808:11-13. In the Lipitor label, among patients having

a median baseline triglyceride level of 565 mg/dL a 20 mg dose of Lipitor reduced triglycerides by 38.7% and reduced LDL-C by 30.4%. DX 1986 (current Lipitor label) at 21; *see also* DX 3007 (2007 Lipitor label) at 11-12. Substantial reductions in both triglycerides and LDL-C were likewise seen with the 10 mg and 80 mg strengths. *Id.* (reporting a 41% reduction in triglycerides and 26.5% reduction in LDL-C, and a 51.8% reduction in triglycerides and 40.5% reduction in LDL-C, respectively). Lipitor was further indicated at these strengths to reduce LDL-C, Apo B, and triglyceride levels. DX 1986 (current Lipitor label) at 1; DX 3007 (2007 Lipitor label) at 14. Consistent with these results, it was known as of March 2008 that "hypertriglyceridemic patients taking the highest doses of the most potent statins (simvastatin and atorvastatin, 80 mg/day; rosuvastatin, 40 mg/day) experience a 35% to 45% reduction in LDL-C and a similar reduction in fasting triglyceride levels." PX 1027 (Mahley et al., *Drug Therapy for Hypercholesterolemia and Dyslipidemia, in The Pharmacological Basis of Therapeutics* 933 (Goodman Gilman et al. eds., 11th ed. 2005) ("Goodman Gilman 2005")) at 22.

335. As of March 2008, it was also "known that EPA could be used with a statin." Toth Tr. 1876:25-1877:2. A person of ordinary skill would also "understand that if you give pure EPA with a statin, you're likely to have an apo B decrease." *Id.* at 1879:21-1880:3 (Toth).

336. For example, Yokoyama 2007 explains that "data for treatment with a combination of n-3 polyunsaturated fatty acids and statins have shown beneficial effects on the lipid profiles of patients with a mixed type of hyperlipidemia." DX 1553 at 1. In JELIS, the authors observed that "EPA did not affect LDL cholesterol concentrations" upon administering purified EPA with a statin as compared to statin therapy alone. *Id.* at 7. In fact, "LDL cholesterol concentrations decreased 25% . . . in both groups." *Id.* at 1.

337. Nakamura likewise discloses a study directed to the "[j]oint effects of HMG-CoA reductase inhibitors and eicosapentaenoic acids on serum lipid profile." DX 1539 (Nakamura et al., Joint Effects of HMG-CoA Reductase Inhibitors and Eicosapentaenoic Acids on Serum Lipid Profile and Plasma Fatty Acid Concentrations in Patients with Hyperlipidemia, 29(1) Int. J. Clin. Lab. Res. 22–25 (1999) ("Nakamura")) at 1. In Nakamura, "pure EPA was given to at least one patient above 500 with a statin." Toth Tr. 1878:11-23.

ix. A skilled artisan would have known that EPA was administered to patients with triglycerides of at least 500 mg/dL.

338. Hayashi reports the daily administration of purified EPA in patients with a serum triglyceride levels above 150 mg/dl. DX 1532 at 4. Specifically, Hayashi investigated the effects of EPA in patients with "familial combined hyperlipidemia (FCH) showing phenotype Ila, Ilb, or IV." *Id.* While Hayashi defined all three phenotypes as "FCH," *id.*, a person of ordinary skill in the art would have understood that phenotype IV refers to the Fredrickson system of classifying lipid disorders. Toth Tr. 1866:10-12. Fredrickson Type IV includes patients with severe hypertriglyceridemia. *See, e.g.*, DX 1986 (current Lipitor label) at 21 (reporting a Lipitor study with a median baseline triglyceride level of 565 mg/dL in patients with Fredrickson Type IV); DX 3007 (2007 Lipitor label) at 11-12; PX 939 (Lovaza statistical review) at 5 (reporting a Lovaza study "in patients with severe hypertriglyceridemia, type IV, with $500 \leq TG \leq 2000$ mg/dl").

339. Table I of Hayashi further reports that, at baseline, the patients in the study had a triglyceride level of 300 ± 233 mg/dl. *Id.* at 5. At least one patient administered EPA in Hayashi had triglyceride levels ≥ 500 mg/dL. Heinecke Tr. 725:21-727:1; Lavin Dep. Tr. 102:24-103:21 (explaining that in Hayashi "you know that there must be at least one subject" with triglyceride levels ≥ 500 mg/dL, and that it is "likely that you have one or two observations above 533").

340. It is undisputed that at least 4 other prior-art studies report administering purified EPA to patients with ≥ 500 mg/dL. Toth Tr. 1862:23-1863:1. For example, Nakamura discloses one patient with a baseline triglyceride level of 6.31 mmol/l, which translates to serum triglycerides of approximately 560 mg/dl. DX 1539 at 2; Heinecke Tr. 733:15-734:3. Saito 1998 likewise teaches administering purified EPA to one patient with serum triglycerides greater than or equal to 500 mg/dl. DX 1546 at 14.

341. In fact, by 1991, purified EPA had already been administered to patients with triglyceride levels above 500 mg/dL. In Takaku, Epadel was administered to at least three patients with triglycerides above 500 mg/dL. DX 1550 at 4, 12, 32; Heinecke Tr. 720:22-721:.23. Individualized data from this study "suggest[ed] that Epadel was significantly lowering triglycerides in this patient population and specifically in patients that had triglycerides above 500 milligrams per

deciliter." Heinecke Tr. 720:22-721:.23. Matsuzawa likewise reported administering Epadel to at least one patient with triglyceride levels above 1,000 mg/dL. DX 1537 (Matsuzawa et al., Effect of Long-Term Administration of Ethyl Icosapentate (MND-21) in Hyperlipidaemic Patients, 7 J. Clin. Therapeutic & Medicines 1801–1816 (1991) ("Matsuzawa")) at 1, 23. Three patients also had triglyceride levels between 400 mg/dL and < 1,000 mg/dL, *id.*, suggesting "there were additional patients above 500 milligrams per deciliter." Heinecke Tr. 723:13-21.

342. The Epadel label likewise does not include an upper limit on triglycerides, and therefore included patients with triglyceride levels ≥ 500 mg/dL. DX 1528 at 1-2; Heinecke Tr. 747:25-748:5. The Epadel label also cites the Takaku and Matsuzawa studies as "main references," DX 1528 at 8-9, and there is no dispute that "Takaku and Matsuzawa included at least one patient with triglycerides above 500." Toth Tr. 1864:18-21.

343. In light of the prior art, a skilled artisan "would have reasonably expected purified EPA to reduce triglycerides above 500." *Id.* at 1860:12-15 (Toth).

x. A skilled artisan would have known that EPA was administered at doses including 4 g/day to reduce triglyceride levels.

344. As of March 2008, there were "a finite number of pure EPA doses that were generally used in the prior art." *Id.* at 1857:1-3 (Toth). Among these, there were "at least six prior art references . . . disclosed the use of 4 grams per day of purified EPA to reduce triglycerides." *Id.* at 1855:20-25 (Toth). For example, Wojenski administered purified EPA at 4 grams/day and was shown to reduce triglycerides. DX 1551 at 2; Toth Tr. 1855:17-19. Grimsgaard 1998 also taught 4 g/day of purified EPA. DX 2264 (Grimsgaard et al., Effects of Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid on Hemodynamics in Humans, 68 Am. J. Clinical Nutrition 52 (1998) ("Grimsgaard 1998")) at 1; Toth Tr. 1854:12-14. And Park taught administering 4 g/day of purified EPA. DX 1545 at 1; Toth Tr. 1855:2-4.

345. Several prior-art studies showed that 4 grams/day of purified EPA was effective at reducing triglycerides. For example, Mori taught that 4 g/day of 96% purified EPA reduced triglycerides by 18.4%, DX 1538 at 2-3, which would lead a skilled artisan to understand that "4 grams pure EPA could reduce triglycerides by about 20 percent." Toth Tr. 1826:24-1827:5.

Woodman 2002 also disclosed a clinical trial in which 4 grams per day of EPA was administered to reduce triglycerides. DX 2263 at 1; Toth Tr.1852:2-5. Woodman 2002 demonstrated that with a 4-gram dose of EPA, triglyceride levels decreased by 19%, or about 20%. DX 2263 (Woodman et al., *Effects of Purified Eicosapentaenoic and Docosahexaenoic Acids on Glycemic Control, Blood Pressure, and Serum Lipids in Type 2 Diabetic Patients with Treated Hypertension*, 76 Am. J. Clinical Nutrition 1007 (2002) ("Woodman 2002")) at 1; Toth Tr. 1852:8-13. Woodman 2003 also disclosed a clinical trial using 4 g/day of EPA, and found that "both EPA and DHA significantly decreased serum triglycerides by a similar extent relative to placebo." DX 2258 (Woodman, et al., *Docosahexaenoic Acid but Not Eicosapentaenoic Acid Increases LDL Particle Size in Treated Hypertensive Type 2 Diabetic Patients*, 26 Diabetes Care 253 (2003) ("Woodman 2003b")) 1; Toth Tr. 1852:25-1853:9.

346. Additional references disclosed administering "about" 4 g/day of EPA. WO '118 taught that "[t]he daily dose in terms of EPA-E is typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day." WO '118 at 35. Grimsgaard 1997 also administered purified EPA at 3.8 g/day, DX 1530 at 1, which a person of ordinary skill in the art would consider to be "about 4 grams per day." Heinecke Tr. 728:11-12.

347. In light of the state of art, Dr. Toth testified that it at least "would be obvious to use 4 grams pure EPA to reduce triglycerides in patients below 500." Toth Tr. 1856:8-10. Dr. Toth further agreed that the prior art "provides reasonable evidence that doses of 2 to 4 grams per day will be at or close to the maximum triglyceride lowering activity of EPA." *Id.* at 1858:4-14 (Toth).

xi. A skilled artisan would have known that EPA was shown to reduce cardiovascular risk.

348. Long before March 2008, it was "suggested that high content of eicosapentaenoic acid (EPA) in diet is linked to low incidence of coronary heart disease." DX 1541 (Nozaki 1992) at 3. Hayashi explained in January 1995 that purified EPA "appear[s] to have an antiatherogenic effect and could be essential in the control of coronary heart disease by lowering plasma lipid content and increasing antithrombotic action." DX 1532 at 3. And in 2000, Mori reported that "[t]here is

considerable evidence to support a protective effect of dietary n-3 polyunsaturated fatty acids against atherosclerotic heart disease." DX 1538 at 1.

349. By 2003, Mochida published a study protocol outlining the rationale and design of the JELIS study, which studied the effects of purified EPA on cardiovascular events. DX 1552 (Yokoyama 2003) at 1. Yokoyama 2003 explains that JELIS was "designed to test the fundamental hypothesis that treatment with highly purified EPA ethyl ester together with lipid lowering with an HMG-CoA reductase inhibitor is more effective than treatment without EPA in reducing major coronary events." *Id.* at 2. Yokoyama 2003 explains that "several megatrials and meta-analyses involving HMG-CoA reductase inhibitors have estimated an approximate 30% reduction of CAD morbidity and mortality compared to none or placebo." *Id.* at 5. Thus, by 2003, investigators were already interested in conducting a clinical trial to assess whether purified EPA might reduce cardiovascular risk over a statin alone. Heinecke Tr. 742:13-743:8.

350. According to Yokoyama 2003, "[w]ith respect to secondary prevention cases, randomized controlled trials such as DART and GISSI showed an inhibitory effect on n-3 PUFAs on cardiovascular events." DX 1552 at 6-7. GISSI-P, for example, "showed that there was a 20% decrease in all death, a 30% decrease in cardiovascular deaths, and a 45% decrease in sudden deaths associated with a daily supplement of n-3 PUFAs (1g daily, EPA/DHA = 1:2) in patients with recent myocardial infarction." *Id.* at 2.

351. Yokoyama 2003 explains, however, that "[i]t has not yet been prove[n] by clinical trials of primary prevention that marine n3- PUFAs reduce the mortality and morbidity of CAD in high-risk subjects." *Id.* Unlike cases of secondary prevention, in which there is "clinical evidence of atherosclerotic coronary artery disease," JELIS thus set out to assess the cardiovascular benefits of EPA in cases of primary prevention, in which there is "[n]o clinical evidence of atherosclerotic artery disease." *Id.* at 3.

352. As for the design of JELIS, approximately two-thirds of the patients recruited were primary prevention patients, who had a lower risk of cardiovascular morbidity and mortality than those in the secondary prevention cohort. *Id.* at 5. All patients were prescribed either pravastatin 10

mg or simvastatin 5 mg "as recommended by [Japan's] Ministry of Health, Labour and Welfare." *Id.* at 4. For patients with uncontrolled cholesterol, the recommended statin doses could be doubled. *Id.*

353. Yokoyama 2003 explains that each patient was to be followed for a maximum of 5 years and defined its primary endpoint as a composite of any "major coronary event[]: sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or coronary artery bypass grafting." *Id.* at 1. All-cause mortality, stroke, peripheral artery disease, and cancer were defined as secondary endpoints. *Id.* Per Yokoyama 2003, while JELIS was open-label (meaning patients knew whether or not they were receiving EPA), all endpoints would be blinded. *Id.*

354. In 2007, Mochida published the results of the JELIS study in an article authored by Yokoyama. DX 1553 (Yokoyama 2007) at 1. The results of the JELIS study were published in the Lancet, *id.*, which is a "top medical journal" and has a "very strong reputation in the medical community." Toth Tr. 1899:20-1900:1; Ketchum Tr. 182:7-9 (characterizing the Lancet as "one of the most prestigious scientific journals"); Heinecke Tr. 748:9-21 (same).

355. Yokoyama 2007 reports that after studying 18,645 patients for a period of 5 years, the JELIS study met its primary endpoint, showing that the addition of EPA on top of a statin provides "a 19% relative reduction in major coronary events." *Id.* In light of the JELIS results, the authors concluded that "EPA is a promising treatment for prevention of major coronary events." DX 1553 (Yokoyama 2007) at 1.

356. As with the rest of this study, the conclusion in JELIS was subject to a "rigorous" peer review process. Toth Tr. 1900:6-8, 1901:10-19. JELIS thus "would have motivated a skilled artisan to run a similar type of study in the United States, to confirm that the results seen in JELIS would apply to a Western population." *Id.* at 1903:11-17 (Toth).

357. JELIS further "provides at least one reason for a skilled artisan to focus on using pure EPA over pure DHA." *Id.* at 1903:5-7 (Toth). Indeed, while there were "a number of DHA studies related to cardiovascular issues[,] . . . [n]one of those were outcome studies" showing a cardiovascular risk reduction. *Id.* at 1903:18-23 (Toth).

358. Mochida further analyzed the JELIS study results in subanalyses. WO '118 reported "a partial analysis of the results obtained in JELIS" and provided a graph on the incidence of cardiovascular events in "patients having the risk factors of a triglyceride (TG) of at least 150 mg/dL and a HDL-C of less than 40 mg/dL." DX 1524 at 13-14, 39. WO '118 reports that in this subgroup of patients with abnormal triglycerides, EPA "significantly suppressed occurrence of cardiovascular events" by 53%. *Id.* at 45-46; *see also id.* at 2 (Fig. 2). The same results were discussed in depth by Saito 2008.[8] DX 1547 (Saito et al., Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS), Atherosclerosis 200 (2008) 135-140 ("Saito 2008")) at 1, 5.

359. As of March 2008 and throughout 2009, several other companies were interested in the cardiovascular benefits of omega-3 fatty acids. Specifically, "there were eight Omega-3 fatty acid trials in progress as of the alleged conception date," which "were still pending when Amarin filed its [patent] application in 2009." Toth Tr. 1897:19-1898:11; PDX 6.29. These eight pending studies "showed that there were high expectations that fish oil would have cardiovascular benefits" as of the alleged priority date. Toth Tr. 1898:12-16. While all eight of these cardiovascular trials failed, a skilled artisan did not know or expect this in March 2008 or February 2009. *Id.* at 1898:17-1899:2. None of these failed studies concerned purified EPA, or addressed patients with severe hypertriglyceridemia. *Id.* at 1899:3-7 (Toth).

4. Prosecution of the asserted claims

360. U.S. Patent No. 8,293,727 ("the '727 patent"), which is not asserted by Amarin in this case, is another patent in the same patent family.[9] Each of the asserted patents share a common specification with the '727 patent, as they are continuations, either directly or indirectly, of the '727

[8] Although Saito 2008 did not publish until June 2008—after Plaintiffs' purported priority date—the conclusions from that reference were reported in 2007 in WO '118. Toth Tr. 1923:1-1924:13.

[9] This family includes several additional unasserted patents. Amarin originally asserted 14 patents in this case. Throughout the case, Amarin has narrowed the asserted patents and claims. A week before trial, on January 3, 2020, Amarin narrowed down the asserted patents and claims from 6 patents and 15 claims to 6 patents and 10 claims.

patent. Thus, statements and actions made during prosecution of the '727 patent are relevant to and were referenced during the prosecution of several of the other asserted patents.

361. The application that issued as the '727 patent was filed on February 9, 2010 and assigned Serial No. 12/702,889 ("the '889 application"). The '889 application claims priority to Provisional Application No. 61/151,291, which was filed on February 10, 2009. The '889 application issued on October 23, 2012 as the '727 patent.

362. Neither the original '889 application nor any of the asserted patents themselves, which all share the same specification, contains any data. *See, e.g.*, DX 1500 ('728 patent). Instead, they recite laundry lists of possible effects on triglycerides, LDL-C, and Apo B, among other blood levels. *Id.* at 16-17. In fact, Amarin did not conduct clinical studies in patients with severe hypertriglyceridemia before filing its patent applications. *See, e.g.*, Manku Dep. Tr. at 79:11-13, 16-19. Amarin had no data of its own until completing the "MARINE" study, which led to Vascepa's FDA approval. *See* DX 1694 (MARINE Study Report). Amarin did not have access to the MARINE data until the results of that study were unblinded in November 2010, long after it filed its patent application. *Id.* at 3.

363. The examiner who reviewed Amarin's patent application repeatedly rejected the pending claims as obvious. For example, while Amarin argued that "actual evidence of record indicates that any change in LDL [in the prior art] is not at all predictive of the impact on LDL in subjects with very high triglycerides," DX 1522 at 72, the examiner rejected these arguments, DX 1587 at 19. According to Amarin, "approved medications for triglyceride lowering in this very high triglceride patient population (e.g. Lovaza, Trilipix, Lopid etc.) all increase LDL-C." DX 1522 at 72. But the examiner explained that "Triplix [sic] (fenofibric acid is structurally and biologically very different from EPA-E," therefore "one cannot extrapolate the results observed with a fibrate (Triplix [sic]) to omega-3-fatty acids like EPA-E." DX 1587 at 19. The effects of fibrates on LDL-C levels therefore "cannot be predictive of a similar behavior (dramatic LDL increase in the very high TG group)" upon administration of EPA in the same patient population. *Id.*

364. In March 2012, the examiner again rejected the claims as obvious over prior art including Mori and Hayashi. DX 1521 at 1640-64, '889 App. File History. The examiner explained

that Mori taught "the administration of 4g/day of EPA-E with a purity of approximately 96%," while Hayashi taught the administration of purified EPA "to individuals with serum TG levels of 300 ± 233 mg/dl (i.e. between 67 mg/dl and 533 mg/dl)." *Id*. at 1644-45. In part because the triglyceride levels in Hayashi "overlap with the claimed ranges of serum TG" of at least 500 mg/dL, the examiner found "a *prima facie* case of obviousness." *Id*. at 1646. "Further, all the other variables claimed, like amount administered (4 g), period of treatment (12 weeks), purity of EPA-E (at least about 96%) are either similar or overlap with the data disclosed by the prior art." *Id*.

365. Amarin tried "to overcome the obviousness rejection" with secondary considerations, but they were "not sufficient." *Id*. at 1661. As the examiner explained, "[t]he prior art presents a strong motivation to treat patients with TG above 500 mg/dl with a purified from of EPA-E (96% or more)." *Id*. Specifically, in light of Hayashi, the examiner found that "[t]he prior art clearly teaches that patients with TG levels from 50 mg/dl up to 530 mg/dl show a significant reduction in TG levels when treated with EPA-E 96%." *Id*. Amarin's alleged secondary considerations were "not enough to overcome such a strong case of obviousness." *Id*. at 1662.

366. Amarin submitted a response in May 2012 that included a declaration from Phillip Lavin, a statistician who disputed the examiner's reading of Hayashi. *Id*. at 1725-28. Dr. Lavin opined that, as a statistical matter, "not even one patient in the study would be expected to have a TG level of 450 mg/dl or higher." *Id*. at 1726. Citing Dr. Lavin, Amarin argued that "it is not reasonable for the Office to allege that any of the subjects in Hayashi have baseline TG levels that overlap with the presently claimed range," and thus there was "no *prima facie* case of obviousness." *Id*. at 1694. Amarin also reasserted that "[e]ven if a *prima facie* case has been established, . . . the evidence previously made of record" on secondary considerations would rebut it. *Id*. at 1703.

367. In September 2012, the examiner issued a "notice of allowance," which included a "statement of reasons for allowance." *Id*. at 1822-35. The examiner first noted that Amarin claimed "a very narrow and specific method." *Id*. at 1829. For example, it requires "TG levels between 500 mg/dl and 1500 mg/dl (very high)," and "at least 12 weeks" of therapy. *Id*. at 1830. Accepting Dr. Lavin's opinion, the examiner found that the prior art did not disclose one of the elements of this method—namely, "[t]he prior art does not teach the administration of ethyl-EPA to patients having

TG levels between 500 and 1500 mg/dl (very high)." *Id.* Neither Amarin nor the examiner cited the other prior-art studies besides Hayashi that had also administered purified EPA to patients with triglycerides greater than 500 mg/dL. FF ¶¶ 298, 338-343.

368. Nevertheless, the examiner still found that "it will be obvious to treat patients having TG above 500 mg/dl with 96% pure ethyl-EPA." *Id.* There is no dispute that in the examiner's view, "the prior art would have motivated a skilled artisan to use purified EPA in patients above 500" and there was "a reasonable expectation of success in using EPA to reduce triglyceride levels below 500." Toth Tr. 1805:17-1806:1.

369. But without a finding that purified EPA was actually given to patients with triglycerides above 500 mg/dL in the prior art, the examiner no longer characterized his obviousness finding as "strong." Instead, he found that Amarin "was able to overcome the . . . obviousness rejection" with expert declarations alleging secondary considerations—namely, an "unexpected" reduction in Apo B, and a "long felt unmet medical need" to reduce triglycerides without raising LDL-C. DX 1521 at 1831-34. The examiner did not cite Kurabayashi, which showed that EPA reduced Apo B. Nor did the examiner acknowledge the teaching in Mori that DHA, but not EPA, increases LDL-C. Nor did the examiner address that Lovaza was frequently administered with statins to address LDL-C increases.

370. During discovery in this case, Dr. Lavin admitted that his opinion was wrong—namely, Hayashi did, in fact, include patients with triglycerides above 500 mg/dL. Thus, he testified that he would "rewrite" his declaration if he could. Lavin Dep. Tr. at 102:24-103:21. In particular, Dr. Lavin explained that, in Hayashi, "you know that there must be at least one subject" with triglyceride levels $\geq$ 500 mg/dL, and that it is "likely that you have one or two observations above 533." *Id.*

5. Amarin and its experts' representations about the prior art

a. Amarin relied on the prior art before the alleged conception date.

371. Amarin alleges that "[t]he inventors of Asserted Patents conceived of the inventions disclosed in the Asserted Claims by March 25, 2008." ECF No. 331 ¶ 24. Even before the alleged

conception date, Ketchum Tr. 205:13-14, Amarin characterized the prior art as disclosing nearly all of the claimed limitations. *See* DX 1814; DX 1829.

372. On March 10, 2008, Amarin recognized in an internal document that "[i]n view of the extensive clinical experience with ultra pure EPA, and with EPA-DHA products, . . . only further limited clinical data are required to confirm the efficacy and safety of ethyl-EPA as a treatment of severe hypertriglyceridemia." DX 1814 at 10. For example, Amarin believed that the "safety and efficacy of ethyl-EPA" was "supported by the publication in the Lancet earlier this year of the JELIS study in which 18000 patients with hyperlipidemia were randomized to receive ethyl-EPA or placebo on background statin therapy." *Id.* at 2. Amarin touted that JELIS showed both "a clinically and statistically significant 19% reduction in the primary endpoint of major coronary events." *Id.* In light of the "extensive clinical experience" with prior-art products, Amarin only required data to "*confirm* the magnitude of effect and the dose response relationship of ethyl-EPA in lowering triglyceride levels in patients with baseline levels above 500 milligrams per deciliter." *Id.* at 10 (emphasis added).

373. An Amarin "business development document" from the same month elaborated on the known benefits of EPA. Ketchum Tr. 190:17-19; DX 1829; *see also* DX 2241 (identifying metadata). This document was created "five days before the alleged date of conception." Ketchum Tr. 189:10-190:4. On March 20, 2008, Amarin's business department explained that it was known that Epadel was "identical" to Vascepa and had "already been approved in Japan" for triglyceride lowering. DX 1829 at 4. Amarin explained that it was "clear from the data generated to date that both Lovaza (EPA/DHA) and Epadel (EPA – identical to AMR101) are effective in lowering triglycerides." *Id.* But according to Amarin, "one differentiating feature is their respective effect on LDL levels." *Id.*

374. Amarin explained that while "Lovaza treatment may result in elevations in LDL in some individuals," in contrast, "Epadel treatment does not appear to have the same [e]ffect on LDL levels." *Id.* at 4-5. "Hence, there's no reference to Epadel treatment causing LDL elevation in Epadel's packaging insert." *Id.* In support, Amarin cited "Mochida's studies on Epadel, as well as independent studies," including Mori. *Id.* at 4-5, 11. Amarin explained that Mori showed that "[s]erum LDL increased significantly with DHA (by 8%) but not with EPA (3.5%)." *Id.* at 11.

According to Amarin, Mori showed that while "both EPA and DHA reduced triglycerides[,] . . . DHA was also associated with an increase in LDL cholesterol." *Id.*

375. In the same March 20, 2008 business development document, Amarin explained that "[s]everal studies have explored and supported the protective effect of omega-3 fatty acids of marine origin against serum lipids and cardiovascular disease," including JELIS. *Id.* at 6-7. Amarin explained that JELIS was a "large scale study" that reported that "the frequency of major coronary events is reduce with EPA (19% p=0.01) given in combination with a statin versus treatment with [a] statin alone." *Id.* at 6. Amarin concluded that "the JELIS study *showed* that the frequency of major coronary events is reduced with EPA (19%) compared to controls." *Id.* at 10 (emphasis added).

b. After the alleged conception date, Amarin continued to characterize the prior art in a manner consistent with Defendants' position to third parties.

376. In a variety of third-party communications to potential partners, investors, FDA, and others, Amarin repeatedly characterized the prior art as teaching the claimed limitations. *E.g.*, DX 1816; DX 1862; DX 1800; DX 1836; DX 2226; DX 2104; DX 2252; DX 2139; DX 2106.

377. On June 16, 2008, Amarin submitted its End-of-Phase 2 Meeting Information Package to FDA for its pre-IND meeting. Ketchum Tr. 221:23 -222:9; DX 1816. In this submission, Amarin explained that a "large body of evidence supports the efficacy of Ethyl-EPA, administered either as monotherapy or add-on to statin therapy, in reducing triglyceride levels in patients with dyslipidemia of varying severity." DX 1816 at 66. Amarin told FDA that over a dozen prior-art studies "demonstrate[d] a decrease in triglycerides of approximately 15 to 40%." *Id.* at 66-67. Among these, Amarin cited Mori to show EPA's "effects on triglyceride levels." *Id.* Amarin cited Mori again to show that "data suggests that doses between 2 and 4 g/day are likely to produce optimal efficacy." *Id.* at 76-77.

378. Amarin also told FDA that while JELIS "was not double-blind, all endpoints and severe adverse events were reviewed and adjudicated in a blinded fashion by an end-point committee." *Id.* at 81. Dr. Ketchum agreed that this was "a positive aspect of the JELIS trial." Ketchum Tr. 224:20-24. Amarin explained that JELIS reported "an overall 19% reduction in major

coronary events," which Amarin attributed to "[a]ll components of the primary endpoint . . . except sudden cardiac death." DX 1816 at 82. Amarin told FDA that while "[t]he rate of all-cause death and stroke were also similar in both treatment arms," a "subanalyses of the JELIS trial showed that the incidence of stroke was actually reduced in the subgroup of subjects who had a previous stroke." *Id.*

379. After summarizing the data from Mori, JELIS, and over a dozen other prior-art studies, Amarin concluded that "[i]n clinical studies performed with Ethyl-EPA to date (including the 18,000 patient JELIS study) there is no evidence of a significant rise in LDL-cholesterol." DX 1816 at 85. At the time Amarin made this statement, "Amarin had not yet conducted any clinical studies in their cardiovascular development program," including the MARINE study. Ketchum Tr. 226:7-13; *see also* DX 1694 at 3. Dr. Ketchum testified that Amarin did not mischaracterize the prior art to the FDA. Ketchum Tr. at 222:7-9.

380. In a partnering presentation dated August 3, 2009, Amarin summarized the prior-art studies supporting the development of Vascepa. *See* DX 1862 at 3. Amarin's presentation include a slide titled "EPA – No LDL Effect," which summarized Mori. *Id.* at 47; *see also* DX 1538 (Mori). Here, Amarin "told its potential partner that Mori teaches that 96 percent EPA, 4 grams per day, has zero percent change in LDL." Toth Tr. 1832:8-1833:1; DX 1862 at 47.

381. In the same August 3, 2009 presentation, Amarin described the JELIS study as providing "[p]roven cardiovascular outcomes" showing that "EPA reduces coronary events." DX 1862 at 54-55. Amarin further highlighted subanalyses from the JELIS study, including Saito 2008's subgroup analysis on patients with elevated TGs and low HDL-C, *see* DX 1547 (Saito 2008), and a subanalysis regarding the "[r]eduction in the [r]ecurrence of [s]troke" in a JELIS subgroup. DX 1862 at 56-57. In light of JELIS and these subanalyses, Amarin conveyed to its potential partner that JELIS was "[s]trongly supportive of improved outcomes in high risk populations," such as those with elevated triglycerides and a history of stroke. *Id.* at 59. Dr. Toth testified that Amarin did not mischaracterize the prior art to its potential partner. Toth Tr. 1832:22-1833:2.

382. In an investor presentation dated March 2010, Amarin told investors that there was a "Clear Differentiation between AMR101 and Lovaza." DX 1800 at 10. Of note, "by March 2010,

Amarin still had no MARINE data." Toth Tr. 1833:4-8. Amarin told its investors that while Lovaza "Elevates LDL-C," Vascepa had "[n]o DHA induced elevation." DX 1800 at 10. In support, Amarin cited multiple prior-art studies. *Id.* at 12-13. As Dr. Ketchum confirmed, "given that this was a presentation for potential investors, Amarin did the best job it could . . . to make sure the representations were accurate." Ketchum Tr. 210:20-211:10. Dr. Toth also testified that Amarin did not mischaracterize the prior art to its investors. Toth Tr. 1834:9-16, 1836:2-17.

383. Amarin told its investors that "Multiple Studies Demonstrate that DHA Raises LDL-C." DX 1800 at 12. Each of these studies published before 2008, and Amarin's characterization of these studies was "a truthful statement that [Amarin] was making to investors." Ketchum Tr. 213:7-18.

384. Amarin also told its investors in March 2010 that "multiple studies demonstrate that EPA is LDL neutral," which was "a truthful statement by Amarin to its investors." Ketchum Tr. 213:19-25, 215:25-216:12; DX 1800 at 13. None of these studies were conducted by Amarin, and each was published before 2008. Ketchum Tr. 214:6-11; DX 1800 at 13. Among the studies showing EPA neutrality, Amarin cited both Mori and Kurabayashi "as a resource" for "investors want[ing] to confirm the statement." Ketchum Tr. 213:19-214:5; DX 1800 at 13. Dr. Toth testified that Amarin did not "mischaracterize[] the Mori and Kurabayashi references to its investors" in this slide. Toth Tr. 1836:2-17.

385. Consistent with Dr. Heinecke's testimony that a POSA would understand Mori's small, non-significant LDL-C increase to teach LDL-C neutrality, Heinecke Tr. 740:18-25, Amarin characterized Mori as showing a "0.00%" change in LDL-C. DX 1800 at 13; *see also* DX 1538 (Mori) at 3. Amarin's characterization that Mori showed a 0% increase in LDL-C was "a faithful reporting of what the authors [of Mori] reported." Ketchum Tr. 214:10-215:3. Dr. Toth agreed. Toth Tr. 1836:2-5, 14-17.

386. Amarin further characterized Kurabayashi as reporting that EPA reduced LDL-C by 5.88%. DX 1800 at 13; *see also* DX 1534 (Kurabayashi) at 3. Amarin likewise believed that this information was an "accurate pulling from the reference." Ketchum Tr. 216:17-24. Dr. Toth agreed. Toth Tr. 1836:6-17.

387. In 2011, the MARINE study results were published in the American Journal of Cardiology. *See* DX 1741 (Bays 2011). In this publication, Amarin again explained that, in "several small previous studies" in the prior art—including Mori—"DHA treatment generally increased LDL cholesterol levels, EPA therapy did not." DX 1741 (Bays 2011) at 7, 9 (citing Mori). Dr. Toth testified that the principal investigator, Dr. Bays, "did not mischaracterize the Mori article" in the MARINE study. Toth Tr. 1838:5-16. The MARINE study also cited Kurabayashi to explain that "[s]maller trials of patients with normal to moderately elevated TG levels suggested that purified EPA might reduce TG levels without increasing the LDL cholesterol levels." DX 1741 (Bays 2011) at 1, 9 (citing Kurabayashi). Dr. Toth again agreed that Dr. Bays "did not mischaracterize the Kurabayashi reference." Toth Tr. 1839:5-18.

388. Thus while the MARINE study concluded that "[a]n unexpected finding was that AMR101 produced no significant increase in the LDL cholesterol levels," *id.* at 7, the principal investigator of MARINE (Dr. Bays) expressed concern that this conclusion "largely guts the current storyline of the paper," DX 1740 at 1. Dr. Bays "was the first author of the MARINE manuscript" and "wrote the first draft" of the article. Bays Dep. Tr. at 151:14-17, 151:21-152:21, 153:3-5, 153:9-19; *see also* DX 1741 (Bays 2011) at 1. On January 14, 2011, while the patent applications were still pending, Amarin emailed Dr. Bays a "minor tweak at the top of page 15" of the draft article and stated the change was "very important to Amarin." DX 1738 at 1. On page 15, Amarin added a sentence to the draft stating that "[t]he unexpected finding in the current trial was that AMR101 did not increase LDL-C levels (no statistically significant change)." DX 1739 at 15. In response, Dr. Bays explained that concluding that EPA's effect on LDL-C "was 'unexpected' is in contradiction to the rest of the manuscript . . . and the reality of this drug development program." DX 1740 at 1. Thus, the published "unexpected finding" remains in the article because it is "important for Amarin," not because it is consistent with the views of the principal investigator.

389. On February 27, 2014, Amarin submitted a formal dispute resolution request to FDA and repeatedly praised the JELIS study. *See* DX 1836. At the time, Amarin sought approval for a second indication for Vascepa in patients with coronary heart disease or a risk equivalent. *Id.* at 6. But FDA rescinded a special protocol assessment relating to FDA's approval of this indication based

on the successful completion of the ANCHOR study and 50% enrollment in REDUCE-IT. *See id.*; Ketchum Tr. 228:23-229:1.

390. After FDA rescinded the special protocol to approve a second indication for Vascepa, Amarin told FDA that the JELIS study "used the same active ingredient as VASCEPA" and "has shown a CV benefit of a statin add-on therapy." DX 1836 at 70. Amarin cited a JELIS subanalysis—reported in WO '118 and Saito 2008, *see* DX 1524 (WO '118), DX 1547 (Saito 2008)—and told FDA that in patients with abnormal TG and HDL-C levels, "EPA treatment suppressed the risk of coronary artery disease by 53% in this higher risk population. DX 1836 at 71. According to Amarin, "this 53% reduction represents a positive subgroup analysis derived from a positive outcome study in which the primary endpoint was successfully met." *Id.*

391. Amarin also justified the design of JELIS and argued "its results should not be dismissed lightly." *Id.* Amarin told FDA that JELIS's open-label design "does not negate its findings." *Id.* Amarin explained that "JELIS was a controlled trial with a PROBE design (prospective, randomized open-label, blinded endpoint evaluation" and studied 18,645 patients. *Id.* As such, "JELIS was a very large, well-designed study with blinded endpoint evaluation that demonstrated a statistically significant reduction in CV risk." *Id.*

392. Amarin further told FDA that while JELIS was "conducted in an exclusively Japanese population," its results "are applicable to the United States population." *Id.* While Amarin acknowledged that JELIS used a "low dose of statins" according to United States guidelines, Amarin reiterated that "[t]he statin therapy in JELIS followed Japanese Atherosclerosis (JAS) guidelines." *Id.* at 73.

393. In conclusion, Amarin told FDA that "JELIS is a very large, well-designed study that demonstrated a significant improvement in its primary endpoint and in subsequent subgroup analyses, such as a 53% reduction in CV events in patients with elevated baseline TG and low baseline HDL-C." *Id.* Dr. Ketchum agreed that this was an "accurate statement to the FDA." Ketchum Tr. 239:2-18. Therefore, in order to "try to convince FDA to take favorable regulatory action," *id.* at 239:19-240:3, Amarin argued that "[t]hese points strongly support the consideration of JELIS study results in evaluating the potential CV benefits of Vascepa therapy." DX 1836 at 81. Dr. Toth confirmed

that he was "not testifying that Amarin overstated the results of the JELIS study to the FDA" in this document. Toth Tr. 1909:11-13.

394. Four months later, on June 24, 2014, Amarin filed a citizen petition to FDA and relied on Mori. *See* DX 2104 at 1, 9. Specifically, Amarin filed a citizen petition requesting that "FDA not approve any ANDA referencing Vascepa that does not meet [certain] bioequivalence testing requirements." *Id.* at 1; Ketchum Tr. 217:6-12.

395. In support of its petition, Amarin told FDA that Mori showed that both EPA and DHA "significantly lowered triglyceride levels," but the "data from that study support . . . that EPA and DHA have differential effects on other well-studied lipid parameters such as LDL-C." DX 2104 at 9; Ketchum Tr. 217:13-218:24. Amarin argued this point to FDA because "DHA in essence would be an impurity in a generic product" and "could lead to different types of lipid effects." Ketchum Tr. 219:3-7. The only study that Amarin cited in support of this argument was Mori, because Mori "found that DHA increased LDL-C, but EPA did not." *Id.* at 219:25-220:9; DX 2104 at 9.

396. As recent as seeking approval of its REDUCE-IT sNDA, Amarin cited JELIS to FDA. On March 29, 2019, in the Summary of Clinical Efficacy of its sNDA, Amarin told FDA that REDUCE-IT "resulted in a 19% relative reduction in the risk of major coronary events despite a relatively small (5%) reduction in TG (Yokoyama 2007), suggesting the effects of EPA therapy on CV outcomes likely go beyond traditional clinical lipid modification." DX 2252 at 9, 62; Ketchum Tr. 243:20-244:19. Amarin characterized its REDUCE-IT study as being "[i]n agreement" with JELIS, "suggest[ing] that the effects of EPA therapy on CV outcomes likely go beyond TG lowering and are distinct from other therapies that lower TG levels." DX 2252 at 62; Ketchum Tr. 244:20-245:7. Amarin also told FDA that JELIS "demonstrated substantial coronary risk reduction similar to Vascepa in REDUCE-IT." DX 2252 at 63.

397. On November 14, 2019—before the FDA Advisory Committee met to consider whether to recommend approving the REDUCE-IT indication—Amarin filed on a Briefing Document explaining why approval was justified. DX 2226 at 1; Ketchum Tr. 245:21-246:4. In the Briefing Document, Amarin told FDA that the REDUCE-IT results were "consistent with the observed risk reduction in the Japan EPA Lipid Intervention Study (JELIS) study." DX 2226 at 6.

Amarin repeated this argument at the Advisory Committee meeting, explaining that JELIS "reported a CV benefit with EPA consistent with REDUCE-IT." DX 2235 at 70. Dr. Toth agreed that these were accurate statements made to FDA. Toth Tr. 1910:8-10.

c. Amarin and its experts have personally praised the JELIS results and/or predicted the REDUCE-IT results.

398. Amarin's employees, consultants, and experts have further either praised the JELIS results or expected REDUCE-IT's outcome based on JELIS.

399. For example, at a 2017 national meeting, Drs. Juliano and Ketchum presented a PowerPoint on REDUCE-IT. *See* DX 1838 at 1; Ketchum Tr. 241:10-242:1. In the presentation, Drs. Juliano and Ketchum presented data to show that the JELIS trial supported an EPA benefit in coronary heart disease. DX 1838 at 8; Ketchum Tr. 242:2-23. In support, Amarin cited both the JELIS study and the subanalyses reported by Saito 2008. DX 1838 at 8; Ketchum Tr. 242:2-23. Drs. Juliano and Ketchum conveyed that the "REDUCE-IT [d]esign is [w]ell-informed" and "incorporates learnings from the positive JELIS study," which was "well designed." DX 1838 at 9; Ketchum Tr. 242:24-243:19.

400. Before the REDUCE-IT results were published, Dr. Budoff stated that he expected a positive outcome for the REDUCE-IT study based on the 53% risk reduction in the JELIS subgroup analysis. DX 2139 at 10. In fact, when asked, "If you had to put odds on this coming out as a win for Vascepa and the REDUCE-IT study . . . what sort of odds of success would you give this study?" Dr. Budoff stated that he would "give [REDUCE-IT] about an 85 percent chance" of being statistically significant and showing a "clinically meaningful risk reduction." DX 2140 at 15.

401. Dr. Elliot Brinton, who served on the steering committee for REDUCE-IT, testified "in a very positive way" about the open-label design of the JELIS study at an FDA Advisory Committee meeting. DX 2106 at 217-219 (Transcript of Endocrinologic and Metabolic Drugs Advisory Committee Meeting, Oct. 16, 2013). Dr. Brinton explained that the "blinded endpoint" design of the JELIS study meant that "the experts didn't know whether the event occurred in one group or the other, and so there's no bias in determining what the endpoint is." *Id.*

402. At the same FDA Advisory Committee meeting, Dr. Michael Miller, who served as a claim construction expert for Amarin in this case, stated that "Dr. Saito found that mixed dyslipidemia patients with triglycerides greater than 150 milligrams per deciliter gained an even greater clinical benefit from the addition of EPA therapy." DX 2106 at 47-49. Dr. Miller attributed the 53 percent reduction in cardiovascular events reported in Saito to the effects of EPA treatment combined with statin and diet therapy. *Id.*

403. Dr. Toth has also praised JELIS on multiple occasions as demonstrating that the addition of EPA to ongoing statin therapy incurred benefit. Toth Tr. 1912:1-6. For example, Dr. Toth was quoted in a 2018 article title "Elevated Triglycerides: Diabetes May Be Predictors of Major Cardiovascular Events" saying: "If the patient's primary residual issue was elevated triglyceride, there is support from the JELIS trial which demonstrated that the addition of EPA to ongoing statin therapy, particularly in patients with triglycerides over 150, incurred benefit." DX 3009; *see also* Toth Tr. 1913:10-1914:3. As Dr. Toth admitted, he "characterized the JELIS trial as demonstrating that the addition of EPA to statin therapy incurred cardiovascular benefit." Toth Tr. 1914:6-10.

404. Similarly, Dr. Toth authored a 2010 article that concluded: "The cardiovascular benefits of omega-3 fatty acids, fish oils, EPA, and DHA are well documented." DX 3020 at 12; *see also* Toth Tr. 1916:5-25. Dr. Toth's article went on to say "[t]here is strong evidence to support the use of statins, fibrates, niacin, BAS and fish oils. . . . The combination of statins with niacin and fish oils has been studied prospectively in the HATS and JELIS trials, respectively. These combinations are effective and provide incremental benefit beyond statin monotherapy." DX 3020 at 13; *see also* Toth Tr. 1917:5-19.

405. In another article containing an interview with Dr. Toth, he is quoted as saying that there is "clinical trial evidence that administering omega-3 fatty acids reduces atherosclerotic cardiovascular events." DX 1709 at 16-17; *see also* 1918:18-1919:7. In this interview, Dr. Toth cited JELIS as one such study, stating that "[t]here is also a nice Japanese study called JELIS in which all the participants were on background statin therapy. The study included both primary and secondary prevention patients. Of note, there was a statistically significant important reduction in the primary composite endpoint, and, once again, in the subgroup of patients with high triglyceride, low HDL,

there was a whopping 53 percent reduction in risk for the primary composite endpoint." DX 1709 at 17; *see also* 1919:8-22.

6. The REDUCE-IT study

406. The REDUCE-IT study was "a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting baseline triglyceride level of 135 to 499" mg/dl and a fasting baseline LDL-C level of 41 to 100 mg/dl. DX 1641 at 1.

407. Each subject in REDUCE-IT had a fasting baseline triglyceride level of 135 to 499 mg/dl. *Id.* at 2, 11. "[B]ecause of the intraindividual variability of triglyceride levels, the initial protocol allowed for a 10% lower triglyceride level from the target lower limit, which permitted patients to be enrolled if they had a triglyceride level of at least 135 mg per deciliter." *Id.* In May 2013, the first protocol amendment "changed the lower limit of the acceptable triglyceride level from 150 mg per deciliter to 200 mg per deciliter, with no allowance for variability." *Id.*

408. Nevertheless, there was a substantial fraction of patients in the REDUCE-IT Study with median triglyceride values <150 mg/dL during the study, given that the inclusion criteria for triglycerides was limited to the screening exam for entry into the study and because triglyceride levels can vary over a wide range. More specifically, about 10% of subjects had triglyceride levels below 150 mg/dl, about 30% had triglyceride levels between 150 and 200 mg/dl, and the remaining subjects had triglyceride levels about 200 mg/dl. *Id.* at 4, Table 1.

409. While a small subset of patients had triglyceride levels that rose above 500mg/dl at some point in time during the REDUCE-IT study due to intraindividual variability, "REDUCE-IT focused on patients with triglycerides below 500." Toth Tr. 1894:12-14. Again, "eligible patients . . . had to have a fasting triglyceride level of 150 to 499 milligrams per deciliter. This is less than 500 milligrams per deciliter." Heinecke 818:18-21. Thus, REDUCE-IT was not "designed to evaluate patients [with] triglycerides above 500" and did not include any patients with a baseline triglyceride level of 500 mg/dl or above. Heinecke Tr. 819:14-16. Dr. Budoff agreed that "REDUCE-IT focused on a different patient population than the patient population" for Defendants' labels. Budoff Tr.

530:16-19. In fact, the MARINE study and REDUCE-IT study, and thus the related indications, involved "completely different patient populations. *Id.* at 589:21-1 (Budoff).

410. Additionally, "[a]ll the patients in REDUCE-IT were taking statins." Toth Tr. 1896:15-17. More specifically, "[e]ligible patients . . . had been receiving a stable dose of a statin for at least 4 weeks." DX 1641 at 2; *see also* Heinecke Tr. 821:9-22. Thus, "in REDUCE-IT, we're talking about patients who are already on a statin for controlling their bad cholesterol." Ketchum Tr. 271:10-13.

411. "REDUCE-IT did not have a monotherapy arm," i.e. an arm with patients not taking a statin. Toth Tr. 1897:5-7. In fact, "it would have been unethical to have just a Vascepa monotherapy arm. The FDA would never allow it because statin therapy is the standard of care for patients in secondary prevention for high risk diabetic patients." *Id.* at 1897:7-10. And approximately 58.6% of the patients enrolled in the treatment arm of the REDUCE-IT Study were diabetics. DX 1641 at 4, Table 1, Bhatt.

412. Patients in REDUCE-IT were randomly assigned to receive either 4 g/day of Vascepa® or placebo (mineral oil). *Id.* at 1-2. "The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infraction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis." DX 1641 at 3. "The key secondary end point [was] a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis." DX 1641 at 3. A total of 8179 patients were enrolled and were followed for a median of 4.9 years. DX 1641 at 1, 5.

413. "The median change in triglyceride level from baseline to 1 year was a decrease of 18.3% . . . in the icosapent ethyl group and an increase of 2.2% . . . in the placebo group." *Id.* at 5. The median reduction [in triglyceride level] from baseline . . . was 19.7% greater in the icosapent ethyl group than in the placebo group." *Id.*

414. "Baseline triglyceride levels (≥ 150 vs. <150mg per deciliter or ≥200 or < 200 mg per deciliter) had no influence on the primary or key secondary efficacy end points." *Id.* at 7. "The attainment of triglyceride levels of 150 mg per deciliter or higher or below 150 mg per deciliter at 1

year after randomization also had no influence on the efficacy of icosapent ethyl as compared with placebo with respect to the primary or key secondary efficacy end point." *Id.*

415. Thus, the REDUCE-IT benefits "occur[ed] irrespective of the attained triglyceride level," and "the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level." DX 1641 at 10; *see also* Heinecke Tr. 817:2-5. As Dr. Toth pointed out, "even if [a subject] didn't normalize [their] triglycerides in [the] trial, [they would] still derive a benefit." Toth Tr. 1624:18-20.

416. With respect to LDL-C levels, "[t]he median change in LDL cholesterol level from baseline was an increase of 3.1% . . . in the icosapent ethyl group and an increase of l0.2% . . . in the placebo group." DX 1641 at 7. REDUCE-IT "found no substantial difference in the benefit" of EPA based on whether patients "had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels." DX 1641 at 7. Thus, "[t]here was no relationship to the change in LDL cholesterol levels to the benefit in terms of cardiovascular risk reduction." Heinecke Tr. 820:22-24.

417. In November 2018, Amarin announced that REDUCE-IT identified a cardiac benefit in patients receiving Vascepa® as compared to placebo. The results show that "[a] primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group." DX 1641 at 1. "A key secondary efficiency end-point event . . . occurred in 11.2% of the patients in the icosapent ethyl group, as compared with 14.8% of the patients in the placebo group." *Id.* at 5. The rate of cardiovascular death was 4.4% in the icosapent ethyl group and 5.2% in the placebo group." *Id.* at 7.

418. According to the Kaplan-Meier plots—which demonstrate results for certain time intervals—in the REDUCE-IT Study Report, the cardiac benefits were not observed until patients had been taking 4 g/day of Vascepa® for a year or more. *Id.* at 132, 134.

419. In other words, there is no "evidence that the cardiovascular risk reduction in REDUCE-IT occurs within 12 weeks . . . Instead there is no divergence [between the treated group and placebo group] in terms of cardiovascular risk until year one, and that difference did not become statistically significant until year two." Heinecke Tr. 819:22-24. Thus, "it takes time to accrue the

[cardiovascular benefit], and if you stop it at four months . . . then you're going to lose that benefit." Toth Tr. 1896:10-14.

420. Based on these REDUCE-IT results, FDA ultimately determined that the cardiac benefit was only present in a subset of patients. Thus, FDA did not approve Vascepa for the wide indication that Amarin sought, but instead approved Vascepa to reduce the risk of "myocardial infraction, stroke, coronary revascularization, and unstable angina requiring hospitalization" in patients that had "elevated triglyceride (TG) levels (≥ 150 mg/dL)," and either an "established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." *Compare* DX 2247 (Vascepa Proposed Label) *with* DX 2248 (Vascepa Label).

421. This narrower indication did not include approval for Vascepa, among other things Amarin sought, to reduce the risk of cardiovascular death. *Id.*; *see also* Ketchum Tr. 248:13-19.

422. "Amarin has separate patents covering the method used in the REDUCE-IT study . . . [and] those patents are not being asserted in this case." Toth Tr. 1895:4-10.

423. Amarin submitted a Form 3542a for the REDUCE-IT sNDA. DX 2250. Through this form, Plaintiffs represented to FDA that only the patents listed relate to Vascepa's REDUCE-IT indication. DX 2299. None of the asserted patents were listed.

424. If Plaintiffs believed that the asserted patents claimed "a method of using [Vascepa] that is the subject of" the REDUCE-IT indication, they would have had to list those patents on the Form 3542a included with their sNDA. 21 C.F.R. § 314.53(b); *see* DX 2250 (sNDA Form 3542a). As shown above, there is no overlap between the patents listed for that indication and the asserted patents. DX 2299.

425. It is not appropriate to compare cardiac outcome studies involving triglyceride-lowering agents to the REDUCE-IT study, especially when Amarin itself has differentiated those studies. Again, as Dr. Budoff testified, the MARINE and REDUCE-IT studies addressed "completely different patient populations." Budoff Tr. 589:21-1.

426. Amarin also points to several other cardiac outcome studies to show that other cardiac output studies failed prior to REDUCE-IT. PDX 6.29. More specifically, Amarin pointed to Alpha Omega, DOIT, OMEGA, ORIGIN, SU.FOL.OM3, R&P, AREDS2, and ASCEND. *Id.*

427. All of the cardiac outcome trials discussed above were initiated before March 2008, the alleged conception date. Toth Tr. 1897:16-25; *see also* PDX 6.29. "And the fact that there were eight cardiovascular studies, as of March 2008, and as of 2009, showed that there were high expectations that fish oil would have cardiovascular benefits." Toth Tr. 1898:12-16; *see also* PDX 6.29.

428. Each of these studies ultimately failed, "[b]ut a skilled artisan, as of March 2008, would not know that any of these trials were going to fail." Toth Tr. 1898:20-24; *see also* PDX 6.29. This is because each of these studies was not completed until after March 2008. Toth Tr. 1898:20-24; *see also* PDX 6.29.

429. Additionally, "none of these trial used pure EPA . . . [a]nd none of these trials were addressing patients with very high triglycerides." Toth Tr. 1899:3-7; *see also* PDX 6.29.

430. More specifically, the ACCORD study looked at the benefit of using fenofibrate in combination with a statin to reduce the risk of cardiovascular events. Fisher Tr. 1013:8-12. Amarin told FDA that "[t]here are two unusual design components of the ACCORD-Lipid protocol that minimize the relevance of this study." DX 1836 (Amarin FDRR) at 44. First, the patients in the REDUCE-IT study were on stabilized statin therapy, while many patients in the ACCORD study were not on statin therapy at baseline. Fisher Tr. 1014:13-1015:13; DX 1836 (Amarin FDRR) at 44. Second, due to a continued drop over the course of the study in triglyceride levels in the placebo group, there were "fewer and fewer subjects who had hypertriglyceridemia" in the placebo group, "so you couldn't really compare the effects of the treatment with regarding to the effects on triglyceride levels." Fisher Tr. 1015:15-1016:24; DX 1836 (Amarin FDRR) at 44.

431. However, Amarin pointed out that a "prespecified subgroup analysis of subjects with both high baseline TG (≥204 mg/dL) and low baseline HDL-C (≤34 mg/dL) suggested a benefit to fenofibrate therapy in this subgroup, with a 31% reduction in the primary endpoint (p=0.057 for the interaction." DX 1836 at 45, Amarin FDRR. The lipid profile of this subgroup in the FIELD study most resembled the lipid profile of the patients in the REDUCE-IT Study. Fisher Tr. 1018:7-1019:7.

432. Another cardiac outcomes study was the ASCEND study. The ASCEND study looked "at two treatments, either single or in combination, low-dose aspirin versus low-dose or 1 gram of

Lovaza on cardiovascular endpoints." Fisher Tr. 1019:14-20. Amarin stated on its website that "differences in study drug, design, and execution clearly differentiate REDUCE-IT from the ASCEND clinical trial." *Id.* at 1020:8-9 (Fisher); DX 2142 (Amarin Website) at 1, 2. While the REDUCE-IT study required that patients be statin-stabilized with high cardiovascular risk, a triglyceride level between 150-499 mg/dL, and hard endpoints adjudicated by experts, the ASCEND study included patients who were not on statins, without evidence of cardiovascular disease, and who self-reported the endpoints on questionnaires. Fisher Tr. 1021:11-1022:15; DX 2142 (Amarin Website) at 2. Moreover, patients in the REDUCE-IT study received 4 grams per day of pure EPA, while patients in the ASCEND study received 1 gram per day of Lovaza.

433. The FIELD study was a cardiac outcomes study with fenofibrate. Fisher Tr. at 1026:3-8. While the overall study did not have a positive outcome, a subgroup analysis of patients with low HDL-C levels (<40 mg/dL in men and <50 mg/dL in women) and triglycerides ≥204 mg/dL "experienced 27% fewer cardiovascular events with fenofibrate treatment." Fisher Tr. 1026:9-1027:12; DX 2126 at 9. This subgroup in FIELD also resembled the lipid profile of the patients in the REDUCE-IT study. Fisher Tr. 1027:22-1028:8.

434. Thus, those cardiac outcome trials with subgroups of patients having lipid profiles similar to that of the REDUCE-IT study exhibited positive reductions in cardiovascular risk.

7. Commercial performance of Vascepa

435. Vascepa® has not been a commercial success—in fact, it has generated annual and cumulative losses through December 2018. Hofmann Tr. 1227:8-1228:3; PX 590; DDX 8.6; Nicholson Tr. 1502:6-8. From launch in 2013, Vascepa® has generated nearly $600 million in cumulative operating losses through 2018. PX 590; Hofmann Tr. 1227:19-24. Additionally, the cumulative operating loss does not include approximately $267 million of expenses associated with R&D and general and administrative ("G&A") expenses prior to the launch of Vascepa®. PX 590; Hofmann Tr. 1227:13-18; DDX 8.6. "Amarin has generated $863 million, nearly a billion dollars, in total losses through 2018 related to the sales of Vascepa." Hofmann Tr. 1227:25-1228:3; *see also* PX 590; DDX 8.6.

436. A portion of Vascepa's operating loss resulted from the cost of its clinical or research and development studies for Vascepa. PDX 5-5. However, the vast majority of these expenses are attributable to the REDUCE-IT study, which involved patients with triglyceride levels below 500 mg/dL and therefore outside the scope of the claims at issue. PDX 5-5, Nicholson Tr. 1533:15-1534:11; 1523:1-5, 9-13; *See* FF ¶ 403.

437. Amarin's expert Dr. Nicholson attempted to perform a net present value calculation for Vascepa based upon averaging the forecasts of five industry analysts over ten years. Nicholson Tr. 1505:8-11. Dr. Nicholson did not contact any of the analysts about their forecasts, and extrapolated two year forecasts (2019-2020) of two of the analysts for an additional eight years. Nicholson Tr. 1506:1-5, 1517:13-1518:12, 1519:5-21; PX 657.

438. Dr. Nicholson confirmed that pharmaceutical companies in general are subject to a high degree of risk, and Amarin and the forecasters themselves stated that Vascepa was subject to a high degree of uncertainty and risk. Nicholson Tr. 1499:9-1500:13, PX 655; Nicholson Tr. 1506:19-1507:22, PX 657 at 5. The analysts themselves showed a wild variation in their forecasts, with one showing a $600M loss and one showing a $7.9B net present value. Nicholson Tr. 1515:20-1514:7, 1521:19-1522:1, DX 2300.

439. Vascepa has "only been able to garner a small single digit percentage of about 3 percent [market share] in the marketplace" for the period 2013 through November 2018. Hofmann Tr. 1235:2-4; *see also* DDX 8.8. "Vascepa has only been able to garner on a cumulative basis about 4.5 million prescriptions compared to the other triglyceride-lowering products" which have totaled 161 million prescriptions. Hofmann Tr. 1233:12-17; *see also* DDX 8.7; PX 391.

440. Moreover, the "vast majority" of Vascepa prescriptions are off-label, to patients with triglyceride levels lower than 500 mg/dl. Hofmann Tr. 1252:17-22; *see also* DDX 8.13; DX 2067; DX 1607. Specifically, from 2013 through 2018, "about three-quarters of the prescriptions are off-label . . . ." Hofmann Tr. 1252:23-1253:6; PDX 5-24; Nicholson Tr. 1497:8-25.

441. "Amarin has undertaken a very extensive and intense marketing campaign with respect to Vascepa. They've used things like direct consumer advertising, detailing, sampling, co-promotion agreements, and we can even study how intense it's been through a measure called Share

of Voice." Hofmann Tr. 1259:20-24. Amarin has "invested very heavily in marketing associated with Vascepa." Hofmann Tr. 1265:17-21; *see also* PX 590; DDX 8.15. Amarin total marketing spend for Vascepa "comes to $575 million, more than half a billion dollars . . . ." Hofmann Tr. 1265:7-16; *see also* PX 590; DDX 8.15. Amarin "was outspending, out-promoting, out-shouting, out-marketing everybody else in the marketplace" with respect to its marketing spend for Vascepa. Hofmann Tr. 1273:16-18; *see also* DDX 8.18, DX 2088. In the period in which Amarin spent $575 million on marketing, it generated about $698 million in net sales, meaning that "82 cents of every dollar has essentially been spent on sales and marketing." Hofmann Tr. 1265:7-21; *see also* PX 590; DDX 8.15; Nicholson Tr. 1525:15-18.

442. Amarin also engages in product detailing for Vascepa. Hofmann Tr. 1267:5-18. Detailing is a marketing technique in which sales representatives visit physicians and provide information about the drug in order to drive prescriptions of the product at issue. *Id.* In late 2012 and early 2013, Amarin hired a sales team of approximately 275 representatives to launch Vascepa® based on the MARINE indication. *Id.* at 1267:19-22 (Hofmann).

443. Amarin entered into a co-promotion agreement with Kowa Pharmaceuticals for Vascepa. Hofmann Tr. 1268:1-4; *see also* DDX 8.16; DDX 8.17; DX 2079. Amarin saw "pretty high double digit growth in prescriptions" after entering into its co-promotion agreement with Kowa. Hofmann Tr. 1270:23-1271:10; *see also* DDX 8.17; DX 1776.

444. Vascepa® has the highest promotional dollar spend for TG reducing brand products, yet has achieved only a three percent prescription share. Hofmann Tr. 1273:16-1274:4; *see also* DX 2088; DDX 8.18.

445. Amarin engages in product sampling for Vascepa. Hofmann Tr. 1275:3-20. Product sampling is used by pharmaceutical companies to influence prescribing behavior and promote the use of various pharmaceutical products. Samples allow physicians and patients to gain familiarity with a drug immediately at no cost to the patient. Hofmann Tr. 1275:8-20. Amarin's use of sampling for Vascepa is "important for them," and Amarin has seen "positive returns" from its sampling. *Id.* at 1276:3-7, 1276:23-1277:7 (Hofmann); *see also* DDX 8.19; DX 2085.

446. The amount of discounts, rebates, and other incentives has increased every year since the launch of Vascepa®. Hofmann Tr. 1278:10-24; *see also* PX 590; DDX 8.20. "[T]hey go from 10 million in the year of launch to about a quarter of a billion dollars in 2018, for a grand total of $631,000,000, which is about half of the total cumulative sales of Vascepa." Hofmann Tr. 1278:20-24; *see also* PX 590; DDX 8.20. The percentage of discounts, rebates, and other incentives relative to gross sales has also increased every year since the launch of Vascepa®. Hofmann Tr. 1279:19-25; *see also* PX 590; DDX 8.21. As of 2018, that percentage reached levels greater than 50 percent. Hofmann Tr. 1279:21-25; *see also* PX 590; DDX 8.21.

447. Amarin also offers a co-payment program to patients. Hofmann Tr. 1280:18-1281:24. "[I]n order to, again, improve patient fulfillment and prescribing behaviors, [Amarin] subsidize[s] that co-pay cost where basically if the co-pay was going to be $75 they may pay a portion of that, and so the patient only has to pay a fraction of the actual co-pay, and so you really insulate the patient from the actual cost of the product. *Id.* at 1281:4-9 (Hofmann).

III. CONCLUSIONS OF LAW

A. Legal standards

1. Infringement

a. General principles

448. "The patentee bears the burden of proving infringement by a preponderance of the evidence. If the patentee fails to meet that burden, the patentee loses regardless of whether the accused comes forward with any evidence to the contrary." *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314 (Fed. Cir. 2011) (quotation omitted).

449. "A method claim is directly infringed only by one practicing the patented method." *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 775 (Fed. Cir. 1993).

450. "To infringe a method claim, all steps of the claimed method must be performed." *Mirror Worlds, LLC v. Apple Inc.*, 692 F.3d 1351, 1358 (Fed. Cir. 2012).

451. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, ¶ 4.[10]

452. "One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim." *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 798 (Fed. Cir. 1990) (quotation omitted).

453. "To prevail on an inducement claim, a patentee must establish that: (1) there has been direct infringement; (2) the defendant, with knowledge of the patent, actively and knowingly aided and abetted such direct infringement. It is well-established that a finding of direct infringement is a prerequisite to a finding of inducement." *Meyer Intellectual Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1366 (Fed. Cir. 2012).

b. Inducement of treatment methods

454. The Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A), "provides an 'artificial' act of infringement that creates case-or-controversy jurisdiction to enable the resolution of an infringement dispute before the ANDA applicant has actually made or marketed the proposed product." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003). "Once jurisdiction is established, however, the substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis, just the same as it is in other infringement suits." *Id.*

455. In Hatch-Waxman cases involving method-of-treatment claims, "the question of induced infringement turns on whether [defendants] have the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products to treat [patients in an infringing manner]. In other words, we ask whether the label encourages, recommends, or promotes infringement. . . . The pertinent question is whether the proposed label instructs users to perform the patented method." *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) (citation omitted). Under this legal standard, "even if [the indicated use] includes [the

[10] Because the Asserted Patents claim priority to applications that predate March 16, 2013, the applicable version of the Patent Act (35 U.S.C. § 100 *et seq.*) predates the amendments enacted by the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

patented use]," there is no inducement if "the proposed ANDA labels do not specifically encourage" the patented use. *Id*.

456. To prove induced infringement, "[m]erely describing the infringing use, or knowing of the possibility of infringement, will not suffice; specific intent and action to induce infringement must be shown." *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019) ("*Horizon*"). If "the label does not require" the patented use that is described, it "does not encourage infringement." *Id.*; *see also Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) ("The question is not just whether instructions describe the infringing mode, but whether the instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent. Merely describing an infringing mode is not the same as recommending, encouraging, or promoting an infringing use, or suggesting that an infringing use 'should' be performed. . . . The label must encourage, recommend, or promote infringement. The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement." (quotations and alterations omitted)); ECF No. 294 at 48 (Amarin's pretrial statement of issues of law quoting the undisputed *Takeda* standard).

457. Thus, a label that merely permits an infringing use, but does not specifically encourage or require that use, does not induce infringement. *See, e.g.*, *Horizon*, 940 F.3d at 701 (affirming holding that "permission does not amount to encouragement"); *Shire LLC v. Amneal Pharms., LLC*, No. 11-3781(SRC), 2014 WL 2861430, at *5 (D.N.J. June 23, 2014), *aff'd in part, rev'd in part on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015) (finding no inducement where defendants' label was "indifferent" to the claimed use and "may be understood to permit an infringing use, but permission is different from encouragement"); *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 188 F. Supp. 3d 367, 377 (D. Del. 2016), *vacated on other grounds*, No. 14-1268-SLR, 2016 WL 7230504 (D. Del. Dec. 14, 2016) ("stating that [a drug] *can* be used for [an infringing use] is not the same as stating [how the drug] *should* be used . . ."); *Otsuka Pharm. Co. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 490 (D.N.J. 2015) ("courts have repeatedly found incidental references to even infringing uses . . . insufficient to constitute instruction or encouragement, as opposed to mere permission"); *see*

also id. at 493 ("the weight of authority has deemed warning and safety information insufficient to constitute inducement, requiring instead that the information be set forth in the 'Uses and Indication' or 'Dosing and Administration' sections."); *United Therapeutics Corp. v. Sandoz, Inc.*, No. 12-CV-01617, 2014 WL 4259153, at *21 (D.N.J. Aug. 29, 2014) ("It is not enough that a user following the instructions may end up practicing the patented method" or "will do so based on their own independent belief that [it] provides a benefit for their patients." (quotation omitted)).

458. These principles apply even if, in practice, the drug is used to infringe 95% of the time. *See In re Depomed Patent Litig.*, No. 13-4057(CCC-MF), 2016 WL 7163647, at *58, *69 (D.N.J. Sept. 30, 2016), *aff'd sub nom. Grunenthal*, 919 F.3d 1333 ("It is not enough that a user following the instructions may end up practicing the patented method"—finding no induced infringement where "less than 5%" of uses were noninfringing and 95% of uses infringed).

459. The same principles apply where the patentee argues that "the product labeling that Defendants seek would inevitably lead some physicians to infringe." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017). As in other inducement cases, "[m]ere knowledge of the acts alleged to constitute infringement is not sufficient." *Id*. at 1368 (quotation omitted). Likewise, "vague instructions that require one to look outside the label to understand the alleged implicit encouragement do not, without more, induce infringement." *Id*. at 1369 (quotation omitted). Courts have found "inevitable" inducement only where the labelling's "instructions are unambiguous on their face and encourage or recommend infringement." *Id*. In that situation, "a label that instructed users to follow the instructions in an infringing manner was sufficient even though some users would not follow the instructions." *Id*. at 1368-69; *see also AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (holding that "[t]he pertinent question is whether the proposed label instructs users to perform the patented method" and affirming, in the context of a preliminary injunction, that the plaintiff established a likelihood of showing that the label's express "language . . . would inevitably lead some consumers to practice the claimed method"); *Otsuka*, 99 F. Supp. 3d at 495 n.29 ("Critically, in affirming the district court's grant of a preliminary injunction, the *AstraZeneca* court relied upon the fact that the generic's label contained *explicit* instructions in the 'Dosage and Administration' section to administer the product in an infringing manner."). By

contrast, where the label does not contain a clear and unambiguous instruction to infringe, "[s]peculation or even proof that some, or even many, doctors would [infringe] is hardly evidence of inevitability." *Takeda*, 785 F.3d at 631, 633.

c. Substantial noninfringing uses

460. Where a product has substantial noninfringing uses, inducement cannot be implied or inferred. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003) ("Especially where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent."); *Horizon*, 940 F.3d at 702 (relying on the fact that the accused product had "substantial noninfringing uses" to hold that the patentee's evidence "does not establish that the proposed label instructs users to perform the patented method") (quotations omitted); *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 (Fed. Cir. 2009) (finding that the patentee's inferred intent argument was "insufficient as a matter of law" because "[e]specially where a product had substantial non-infringing uses, intent to induce infringement cannot be inferred").

461. The patentee "ha[s] the burden to prove the lack of substantial non-infringing uses," *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1363 (Fed. Cir. 2012), which include "any use that is not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323, 1337 (Fed. Cir. 2012) (quotation omitted). "In a pharmaceutical case, the noninfringing use must be in accordance with the use for which the product is indicated." *Grunenthal*, 919 F.3d at 1340. Here, the Court has already found that substantial noninfringing uses exist for all asserted claims. ECF No. 278 at 12-13.

d. Scope of FDA approval

462. Induced infringement cannot be found if the FDA has not approved the method of use recited in the asserted patent claim. *See, e.g.*, *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1332 (Fed. Cir. 2003) ("a method of use patent holder may not sue an ANDA applicant for induced infringement of its patent, if the ANDA applicant is not seeking FDA approval for the use claimed in the patent and if the use claimed in the patent is not FDA-approved"); *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1326 (Fed. Cir. 2012) ("[T]he FDA has not approved [the patented] use

and th[us] the defendants cannot be held liable for infringement of the patent."); *AstraZeneca Pharms. LP v. Apotex Corp.*, 669 F.3d 1370, 1379 (Fed. Cir. 2012) ("[A] patented method of using a drug can only be infringed under § 271(e)(2) by filing an ANDA that seeks approval to market the drug for that use."); *Warner-Lambert*, 316 F.3d at 1354-55 ("[I]t is not an act of infringement to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA.").

463. Under FDA regulations, "[i]ndications or uses must not be implied or suggested in other sections of the labeling if not included" in the "[i]ndications and usage" section. 21 C.F.R. § 201.57(c)(2)(iv). Specifically, the "clinical studies" section "must not imply or suggest indications or uses or dosing regimens not stated in the 'Indications and Usage' or 'Dosage and Administration' section." *Id*. § 201.57(c)(15)(i); *accord* DX 1681 (FDA guidance on Clinical Studies section) at 6.

464. FDA regulations also make clear that the "[i]ndications and usage" section "must include" any "specific tests [that] are necessary for selection or monitoring of the patients who need the drug" and any "specific conditions that should be met before the drug is used on a long term basis." 21 C.F.R. § 201.57(c)(2)(i)(C), (F).

465. Similarly, FDA guidance provides that the "Indications and Usage" section must set forth the "[s]elected patient subgroups or disease subpopulations for whom the drug is approved." PX 573 at 11. For example, the Indications and Usage section should state whether approval is limited to "patients previously treated with other therapies." *Id*. More generally, "the indication should clearly convey the patient population for which the drug is approved." *Id*.

466. The Hatch-Waxman "Act permits generic manufacturers to file ANDAs directed to a subset of FDA-approved indications and even provides a mechanism for ANDA applicants to affirmatively carve out patented indications." *AstraZeneca*, 669 F.3d at 1381. The argument that "restricted generic labeling ignore[s] market realities because even if a generic drug is formally approved only for unpatented uses, pharmacists and doctors will nonetheless substitute the generic for all indications once it becomes available" is irrelevant under the Hatch-Waxman Act and has been rejected by the Federal Circuit as "unpersuasive." *Id*. at 1380; *see also* 21 U.S.C. § 355(j)(2)(A)(viii); *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 406 (2012) (noting that the Hatch-

Waxman Act "allows the generic company to place its drug on the market . . . for a subset of approved uses").

2. Obviousness

a. General principles

467. A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a).

468. Whether a patent claim is invalid as obvious is ultimately a question of law based on four underlying questions of fact: (a) the level of ordinary skill in the pertinent art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claims at issue; and (d) secondary considerations, which are also known as objective indicia of nonobviousness. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

469. "[T]he patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). "The 'clear and convincing' standard is an intermediate standard which lies somewhere in between the 'beyond a reasonable doubt' and the 'preponderance of the evidence' standards of proof. Although an exact definition is elusive, 'clear and convincing evidence' has been described as evidence that 'place[s] in the ultimate factfinder an abiding conviction that the truth of its factual contentions are highly probable.'" *Id*. at 1359 n.5 (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

470. Notwithstanding this evidentiary standard, obviousness is judged under "an expansive and flexible approach." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007) (reversing judgment of nonobviousness). An obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. Where a claim "simply arranges old elements with each

performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quotation omitted).

471. The Supreme Court has thus emphasized "the need for caution in granting a patent based on the combination of elements found in the prior art," because "a patent for a combination which only unites old elements with no change in their respective functions obviously withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men." *Id*. at 415-16 (quotation and alteration omitted).

472. "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *Id*. at 419.

473. Where "every limitation of the asserted claims [is] disclosed in the cited references," the question of whether the differences between the prior art the claims are obvious generally turns on "whether a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013) (reversing judgment of nonobviousness).

474. "It is a long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (quotation omitted). "What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *KSR*, 550 U.S. at 419.

475. Where "the PTO did not have all material facts before it, its considered judgment may lose significant force," and courts should "consider that fact when determining whether an invalidity defense has been proved by clear and convincing evidence." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 111 (2011); *see also KSR*, 550 U.S. at 426 ("We need not reach the question whether the failure to disclose [facts or prior art] during the prosecution of [a patent] voids the presumption of validity given to issued patents. . . . We nevertheless think it appropriate to note that the rationale underlying the presumption—that the PTO, in its expertise, has approved the claim—seems much

diminished here."); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1379 (Fed. Cir. 2005) (finding reversible error where the "district court failed to appreciate that the prosecution history of the relevant patents, while not establishing inequitable conduct, casts some doubt on the final examiner's conclusion that the claimed [invention] produces unexpected results sufficient to overcome a prima facie case of obviousness.").

b. Prior conception

476. Conception is "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 967 (Fed. Cir. 2014) (quotation omitted).

477. "The issue of the conception date of an invention is a legal conclusion based on underlying factual findings." *Id*. "While defendants bear the burden of persuasion to show" invalidity, "the patentee nevertheless must meet its burden of production to demonstrate an earlier conception date" than the filing date of the patent. *Id*.; *see also Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1322 (Fed. Cir. 2013) ("After an accused infringer has put forth a prima facie case of invalidity, the burden of production shifts to the patent owner to produce sufficient rebuttal evidence to prove entitlement to an earlier invention date."); *cf. Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996) ("Had [the inventor] not come forward with evidence of an earlier date of invention, . . . [the] invention date would have been the filing date of his patent.").

478. Acknowledgment by a patent challenger's expert witness that the patentee "asserts priority as of that date . . . does not constitute an agreement or concession that the claimed priority date is accurate." *Purdue Pharma L.P. v. Iancu*, 767 F. App'x 918, 925 (Fed. Cir. 2019) (affirming obviousness determination as of the August 2002 priority date, even though the invalidity expert's opinions were based on the patentee's purported priority date of August 2001).

479. As the Court has recognized, "under governing law," "a patent challenger does not need to present any evidence as to priority date when the plaintiff has not met its burden to establish a particular priority date." ECF No. 315 at 7 (citing *Purdue*, 767 F. App'x at 924-25).

480. In cases "where an inventor tries to prove prior conception, the inventor's testimony, standing alone, is insufficient to prove conception—some form of corroboration must be shown.

[Courts] have treated uncorroborated testimony from an alleged inventor asserting priority with skepticism." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1346 (Fed. Cir. 2017) (quotation omitted).

c. Scope and content of prior art

481. The prior art includes what is "described in a printed publication in this or a foreign country." 35 U.S.C. § 102(a), (b).

482. "[T]he scope of the relevant prior art . . . includ[es] that reasonably pertinent to the particular problem with which the inventor was involved." *In re GPAC Inc.*, 57 F.3d 1573, 1577 (Fed. Cir. 1995) (quotation omitted). "A reference is reasonably pertinent if, even though it may be in a different field of endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* at 1578 (quotation omitted). "If a reference disclosure relates to the same problem as that addressed by the claimed invention, that fact supports use of that reference in an obviousness [finding]." *Id.* (quotation omitted).

483. "Under § 103, . . . a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003); *accord Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991).

484. "All the disclosures in a reference must be evaluated, including nonpreferred embodiments." *In re Mills*, 470 F.2d 649, 651 (C.C.P.A. 1972); *see also Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (holding that "all disclosures of the prior art, including unpreferred embodiments, must be considered").

485. A prior-art reference that is "not published in peer-reviewed journals or authored by one skilled in the art" nevertheless may "support the conclusion that [the] claims . . . are invalid as obvious." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1374-75 (Fed. Cir. 2005).

486. Arguments against obviousness "lack merit [where] they attack the disclosures of [prior-art] references individually. A finding of obviousness, however, cannot be overcome by attacking references individually where the rejection is based upon the teachings of a combination of references." *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1050 (Fed. Cir. 2019) (quotation omitted).

487. In addition to prior-art references that are combined to arrive at the asserted claims in an obviousness analysis, "[a]rt can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015); *see also Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (vacating nonobviousness finding that "narrowly focus[ed] on the four prior-art references cited" in obviousness combinations and "failed to account for critical background information that could easily explain why an ordinarily skilled artisan would have been motivated to combine or modify the cited references to arrive at the claimed inventions").

488. In particular, background prior art can be used to rebut a patentee's argument that a skilled artisan would not have combined the asserted references. *See Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1193 (Fed. Cir. 2019) ("Persion asserts that Alvogen had expressly dropped an obviousness combination that included the FDA's statement and thus Persion was deprived of an adequate opportunity to respond to the statement during trial. However, the district court relied on the FDA's statements not as part of a prior art combination, but only in rebutting Pernix's assertion that there was no motivation to combine the teachings of Devane with the hydrocodone-acetaminophen formulations described in Jain and the Vicodin and Lortab labels.").

489. Documents that are not themselves prior art, such as internal company documents and confidential representations to the FDA, may also provide evidence of the state of the art that is relevant to obviousness. *See, e.g.*, *Pfizer*, 480 F.3d at 1365 (finding obviousness and relying on the fact that "there is a suggestion in Pfizer's supplemental filing with the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose"); *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 766 & n.12 (Fed. Cir. 1988) (relying on "internal memorandum" that "was not technically 'prior art'" as "evidence [of what] others of ordinary skill in the art had" done); *Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572, 1580-81 (Fed. Cir. 1983) (holding that "unpublished internal criteria . . . , though not technically prior art, were, in effect, properly used as indicators of the level of ordinary skill in the art to which the invention pertained"); *Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018) (holding that reliance on non-prior art was "permissible, as it supports and explains [the] position that a [skilled artisan] would have thought

[the claimed invention] worthy of investigation as of the priority date"); *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337-38 (Fed. Cir. 2004) (holding that documents which were not publicly available nevertheless "can be understood to suggest that one of ordinary skill in the art would have been motivated to combine" other references that were in the prior art).

d. Motivation to combine

490. Although it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements," a court "need not seek out precise teachings directed to the specific subject matter of the challenged claim." *KSR*, 550 U.S. at 418.

491. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id*. at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id*. at 420.

492. "Far from requiring evidence of an explicit motivation to combine," the Federal Circuit has likewise made clear that "an *implicit* motivation" is enough. *DyStar Textilfarben GmbH & Codeutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1366 (Fed. Cir. 2006) (reversing judgment of nonobviousness). The Federal Circuit has "repeatedly held" that a combination of prior-art references may be obvious "even absent any hint of suggestion in the [prior art] references themselves." *Id.* at 1368. A court that requires the prior art "clearly and unequivocally [to] disclose" a "motivation to combine" therefore "err[s] by taking an overly cramped view of what the prior art teaches." *Allergan*, 754 F.3d at 963-64 (reversing judgment of nonobviousness). In other words, "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention." *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997).

493. The Federal Circuit has repeatedly made clear that in order to have a motivation to practice a claimed invention, the prior art does not need to suggest that the claimed invention was the best solution available, or superior to other options in the prior art:

> [O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention. The question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the *most desirable* combination available. . . . Thus, a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination.

In re Fulton, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (internal quotation omitted; collecting cases).

494. Federal Circuit precedent "does not require that the motivation be the *best* option, only that it be a *suitable* option." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014); *see also E.I. du Pont De Nemours & Co. v. MacDermid Printing Sols., L.L.C.*, 657 F. App'x 1004, 1014 (Fed. Cir. 2016) (for motivation, "the legally proper question is whether [the claimed solution] would be a suitable option in *some* respects, not necessarily in *every* respect."); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (to provide a motivation, "it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have *similar properties* to the old") (emphasis added; quotation and alteration omitted) (reversing judgment of nonobviousness).

495. A given course of action is obvious if it was actually done in the prior art. *See Nalpropion Pharm., Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1344, 1354-55 (Fed. Cir. 2019) (rejecting the argument that a skilled artisan would not have combined two drugs: "The inescapable, real-world fact here is that people of skill in the art *did combine* bupropion and naltrexone for reductions in weight gain and reduced cravings—goals closely relevant to weight loss. . . . Thus, we conclude that skilled artisans would have been motivated to combine the two drugs for weight loss with a reasonable expectation of success.") (reversing judgment of nonobviousness).

496. "The desire to decrease the risks of administering a drug with adverse side effects . . . is a specific motivation to improve the prior art." *Celgene Corp. v. Peter*, 931 F.3d 1342, 1354 (Fed.

Cir. 2019). "The fact that there is no long-felt, unmet need [for such improvement] does not necessarily mean that there is no motivation to improve [the prior art]." *Id*. at 1353.

497. With respect to inventions that involve purifying active ingredients, the Federal Circuit has noted that "isolation of interesting compounds is a mainstay of the chemist's art." *Aventis*, 499 F.3d at 1302. "If it is known how to perform such an isolation, doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Id*. (quoting *KSR*, 550 U.S. at 419-20). "[I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified." *Id*. at 1301.

498. "The motivation to combine inquiry is not limited to what products are forthcoming or currently available on the market. Particularly given the lengthy FDA approval process, the pharmaceutical industry is no exception." *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1324 (Fed. Cir. 2017) (reversing judgment of nonobviousness). As a result, "a lack of FDA approval cannot negate an otherwise apparent motivation to formulate a product." *Id*. at 1326.

499. "There is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval. Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications." *Allergan*, 726 F.3d at 1292 (reversing judgment of nonobviousness).

500. In determining whether it would have been obvious to practice a method of using a particular compound as a drug, there is no need to show that a skilled artisan would have selected the claimed compound over other prior-art compounds. *See Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019) ("[The patent-in-suit] does not claim the everolimus compound itself, but rather methods of using the compound. This case therefore does not require lead compound analysis or analysis of whether a particular dose in a range of prior art doses would have been obvious. . . . To the extent the district court required a showing that a person of ordinary skill would have selected everolimus over other prior art compounds, it erred.").

501. Courts apply a specific framework in determining whether there is a "motivation to select" a dose or concentration from a range of potential choices in the prior art: "where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (reversing finding of nonobviousness).

e. Reasonable expectation of success

502. "As stated above, an obviousness determination requires not only the existence of a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination. While the definition of 'reasonable expectation' is somewhat vague, [Federal Circuit] case law makes clear that it does not require a *certainty* of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Thus, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success"— "only a reasonable expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d at 1364; *see also, e.g.*, *PAR*, 773 F.3d at 1198 ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success."); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."); *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness.").

503. Difficulties in receiving FDA approval "are not particularly probative with respect to obviousness" because "[t]here is no requirement that one of ordinary skill have a reasonable expectation of success in developing" an FDA-approved drug that embodies the asserted claims. *Allergan*, 726 F.3d at 1292. Rather, "the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention." *Id.*; *see also Intelligent Bio-Sys., Inc.*

v. Illumina Cambridge Ltd., 821 F.3d 1359, 1367 (Fed. Cir. 2016) ("The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention"—the "correct inquiry" is whether there is "a reasonable expectation of achieving what is claimed in the patent-at-issue").

504. The fact that later testing was needed to verify an expectation does not mean that there was no reasonable expectation of success. "Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007) (reversing jury verdict of nonobviousness). "A supplemental study does not imply lack of awareness of the likely result; rather, studies are frequently conducted to confirm what is suspected to be true. An incentive to conduct a confirmatory study frequently exists even when one has every reason to expect success." *Soft Gel Techs., Inc. v. Jarrow Formulas, Inc.*, 864 F.3d 1334, 1342 (Fed. Cir. 2017); *see also Pfizer*, 480 F.3d at 1367 (reversing judgment of nonobviousness where "one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation" with testing); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (obviousness "does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice.").

505. Relatedly, there is "no authority from the Supreme Court or [the Federal Circuit] requiring as a matter of law, for reasonableness of an expectation of success, testing of specific doses versus placebo that shows the relevant result with statistical significance." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018). On the contrary, "a person of skill in the present context *can* draw reasonable inferences about the likelihood of success even without a perfectly designed clinical trial showing a statistically significant difference." *Id.* at 1334.

506. It is clear error for a court to find that there was no reasonable expectation of success based on a lack of clinical data in the prior art, where the patent-in-suit has no such data. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (reversing judgment of nonobviousness—"the district court clearly erred in finding any difference between the claimed

invention and the [prior art]" based on the prior art's lack of clinical data, where the asserted "patent sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent" and thus "adds nothing beyond the teachings" of the prior art); *Hoffmann-La Roche*, 748 F.3d at 1331 (affirming obviousness and rejecting the argument that the prior art lacked "antifracture efficacy" data where the asserted "patents do not themselves present data demonstrating antifracture efficacy"); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (reversing judgment of nonobviousness and rejecting the "argu[ment] that [the prior art] would not give a skilled artisan an expectation of success" for the claimed drug's safety, because "neither does the [asserted] patent," which was "not based on testing in humans"); *In re Copaxone Consol. Cases*, 2017 WL 401943, at *17 (D. Del. Jan. 30, 2017), *aff'd*, 906 F.3d 1013 (Fed. Cir. 2018) ("It would constitute clear error for the court to discredit the [prior-art] reference for the same lack of dosing frequency clinical data from which the patents-in-suit suffer.") (citing *Merck*, 395 F.3d at 1374).

f. Obvious to try

507. The Supreme Court has rejected the argument "that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try." *KSR*, 500 U.S. at 421 (quotation omitted). "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*; *see also Hoffmann-La Roche*, 748 F.3d at 1332 (claimed "dose was obvious to try" where "[t]here was a need to solve the problem of patient compliance by looking to less-frequent dosing regimens" and "there were only a finite number of identified, predictable solutions") (quotation omitted).

508. Where there is only one difference between the claimed invention and a prior-art reference, the obvious-to-try inquiry focuses on the available options with respect to the claimed invention's point of novelty. *See Google LLC v. Koninklijke Philips N.V.*, — F. App'x —, 2020 WL 54183, at *4 (Fed. Cir. Jan. 6, 2020) (reversing judgment of nonobviousness—a "wide-scope inquiry

into all [ ] possibilities does not fairly reflect the point of *KSR*'s relevant discussion as it applies to a case, like this one, in which it is not disputed that a relevant artisan would in fact be studying a particular piece of prior art in thinking about the artisan's own possible further work. In that situation, the Court's declarations about 'mere substitution of one element for another known in the field,' with 'predictable results,' indicate that the obvious-to-try inquiry at least sometimes must focus on known options at what is undisputedly the sole point of novelty in the claim at issue.") (quoting *KSR*, 550 U.S. at 416)).

509. In evaluating whether a claimed solution was obvious to try, the question is not how many solutions were theoretically possible, but how many were already identified in the prior art. *See In re: Copaxone*, 906 F.3d at 1026 (finding claimed dosage obvious to try—"Although the universe of potential GA doses is theoretically unlimited, the universe of dosages in the prior art that had clinical support for being effective and safe consisted of only two doses: 20mg and 40mg.").

510. Similarly, the question of whether there was a finite number of identified solutions does not focus on "all possibilities in a field unreduced by the prior art," but instead turns on the number of plausible solutions to which the skilled artisan was "guided" by the prior art. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009) (finding claimed drug formulation obvious to try where "a person having ordinary skill in the art has reached a crossroads where he must choose between two known options. . . . This is a finite number of identified, predictable solutions. . . . The prior art would have funneled the formulator toward these two options; he would not have been required to try all possibilities in a field unreduced by the prior art."); *see also Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 14-882-LPS, 2017 WL 1199767, at *32 (D. Del. Mar. 31, 2017), *aff'd*, 903 F.3d 1310 (Fed. Cir. 2018) (finding claimed drug dose obvious to try where the prior art "reduced the set of plausible doses" "to a fairly narrow band").

g. Conflicting evidence and teaching away

511. "Obviousness, unlike anticipation, does not require a prior art successful formulation," and can be found even where there is "conflicting evidence as to motivation and reasonable expectation of success." *Merck Sharp & Dohme Corp. v. Wyeth LLC*, — F. App'x — , 2019 WL 6320454, at *3 (Fed. Cir. Nov. 26, 2019).

512. "A reference does not teach away if it does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *Galderma*, 737 F.3d at 739 (alteration and citation omitted); *accord, e.g.*, *Fulton*, 391 F.3d at 1201.

513. The fact "that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex*, 407 F.3d at 1380. "A reference does not teach away, however, if it merely expresses a general preference for an alternative invention." *Galderma*, 737 F.3d at 738.

514. "[T]he teaching away inquiry does not focus on whether a person of ordinary skill in the art would have merely *favored* one disclosed option over another disclosed option." *Bayer*, 874 F.3d at 1327. "When there are only two possible formulations and both are known in the art at the time, the fact that there may be reasons a skilled artisan would prefer one over the other does not amount to a teaching away from the lesser preferred but still workable option." *Id*.

515. Thus, "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012); *see also Biocraft*, 874 F.2d at 807 (the fact "[t]hat the [prior art] discloses a multitude" of other "combinations does not render [a] particular formulation less obvious"); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("[A] known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.").

516. The fact that other potential inventions also would have been obvious does not render a claimed invention any less obvious. *See ACCO Brands Corp. v Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) ("even if one possible obvious combination falls outside of the claims, it fails to undercut the fact that the other possible obvious combination lies within their scope").

517. In general, the prior art does not teach away from using products that were on sale and recognized as safe in the prior art. *See Aker Biomarine Antarctic AS v. Rimfrost AS*, 786 F. App'x 251, 255 (Fed. Cir. 2019) ("Here, perhaps most probative is the fact that, at the time of the invention, encapsulated krill oil was on sale and generally recognized as safe. Given that krill oil with ether phospholipids was on sale and, absent any evidence suggesting that the capsules were somehow pro-

inflammatory or dangerous, the Board's finding that the art did not teach away from supplements containing krill oil is certainly supported by substantial evidence.").

518. "Evidence concerning whether the prior art teaches away from a given invention must relate to and be commensurate in scope with the ultimate claims at issue." *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1381 (Fed. Cir. 2017).

519. Even where one or more references teaches away, or the evidence of obviousness is conflicted, that fact alone is not dispositive to the obviousness inquiry:

> However, obviousness must be determined in light of all the facts, and there is no rule that a single reference that teaches away will mandate a finding of nonobviousness. Likewise, a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine. . . . Where the prior art contains apparently conflicting teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill considering the degree to which one reference might accurately discredit another.

Medichem, 437 F.3d at 1165 (quotations and alterations omitted); *see also Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 834 (Fed. Cir. 2015) (rejecting teaching away based on "isolated prior art disclosures" in "two prior art references" because "the prior art as a whole . . . d[id] not teach away").

h. Secondary considerations (objective indicia)

520. "Evidence of secondary considerations" is "part of the totality of the evidence that is used to reach the ultimate conclusion of obviousness." *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (quotation omitted).

521. "While th[e] burden of persuasion remains with the [patent] challenger, a patentee bears the burden of production with respect to evidence of secondary considerations of nonobviousness." *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018).

522. The purpose of "[s]econdary considerations [is to] help inoculate the obviousness analysis against hindsight." *ZUP*, 896 F.3d at 1373 (quotation omitted); *see also Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (the purpose of "[s]econdary considerations of nonobviousness" is to "check against hindsight bias").

523. The Federal Circuit has repeatedly made clear, however, that "a strong showing of obviousness may stand even in the face of considerable evidence of secondary considerations." *ZUP*, 896 F.3d at 1373 (quotation omitted); *see also, e.g.*, *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008) (reversing judgment of nonobviousness—"objective evidence of nonobviousness simply cannot overcome . . . a strong prima facie case of obviousness"); *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013) ("[W]here a claimed invention represents no more than the predictable use of prior art elements according to established functions, . . . evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness."); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (holding that, "given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion that [the claim] would have been obvious."); *DyStar*, 464 F.3d at 1371 ("secondary considerations of nonobviousness are insufficient as a matter of law to overcome our conclusion that the … claim [at issue] would have been obvious."); *Richardson-Vicks*, 122 F.3d at 1484 ("The unexpected results and commercial success of the claimed invention, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious.").

i. Nexus and scope requirements

524. "[E]vidence of secondary considerations must have a 'nexus' to the claims, i.e., there must be a legally and factually sufficient connection' between the evidence and the patented invention." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (quotation omitted) (vacating judgment of nonobviousness); *see also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) ("The term 'nexus' is often used, in this context, to designate a legally and factually sufficient connection between the proven success and the patented invention, such that the objective evidence should be considered in the determination of nonobviousness.").

525. "It is the established rule that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Allergan*, 754 F.3d at 965 (quotation omitted; reversing judgment of nonobviousness). Where the evidence is "not

commensurate with the full scope of the patent's claims," the evidence "lack[s] a nexus with the scope of the [asserted] patent's claimed invention." *Id*.

526. "Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

527. Evidence that does not result from practicing the asserted claims lacks a nexus to, and is irrelevant to, whether the claims are obvious. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 n.42 (Fed. Cir. 1985) (if "products were not covered by the [asserted] patents, [ ] then the secondary considerations [based on those products] would not have had any relevance to the obviousness/nonobviousness determination"); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) ("secondary considerations may presumptively be attributed to the patented invention only where the marketed product embodies the claimed features, and is coextensive with them") (quotation omitted); *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1366 (Fed. Cir. 2001) (secondary considerations based on "copying Amazon's '1-Click®' feature is legally irrelevant unless the '1-Click®' feature is shown to be an embodiment of the claims").

528. Even "impressive" evidence of secondary considerations is not "entitled to weight" unless "it is relevant to the claims at issue." *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

529. "[T]he patentee" bears the "burden of production to demonstrate a nexus between the claimed [invention] and the secondary considerations." *MRC Innovations, Inc. v. Hunter Mfg., LLP*, 747 F.3d 1326, 1336 (Fed. Cir. 2014).

530. A patentee is only "entitled to a rebuttable presumption of nexus between the asserted evidence of secondary considerations and a patent claim if the patentee shows that the asserted evidence is tied to a specific product and that the product *is* the invention disclosed and claimed." *Fox Factory*, 944 F.3d at 1373 (quotation omitted). In other words, presuming nexus is appropriate only "when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them." *Id*. (quotations omitted). "Although [the Federal Circuit] do[es] not require the patentee to prove perfect

correspondence to meet the coextensiveness requirement, what [the Court] do[es] require is that the patentee demonstrate that the product is essentially the claimed invention." *Id*. at 1374 (reversing finding of presumed nexus).

531. "Where a product embodies claims from two patents, a presumption of nexus can be appropriate only if the claims of both patents generally cover the same invention." *Id*. at 1377. Put differently, where "the product embodie[s] at least two patented inventions, [ ] the burden thus remain[s] on the patentee to show that the product's success was due to the invention claimed in the patent asserted in the case." *Id*. at 1375 (citation omitted); *see also Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010), *vacated on other grounds*, 374 F. App'x 35 (Fed. Cir. 2010), *reinstated in relevant part*, 649 F.3d 1276 (Fed. Cir. 2011) ("This is not a situation where the success of a product can be attributed to a single patent, because [the patentee's] product embodied at least two patents: the [claimed] patent and [another] patent. . . . As such, there is no presumption that the product's success was due only to the [claimed] patent.").

ii. Long-felt and unmet need

532. A motivation to improve the prior art does not, without more, establish a long-felt and unmet need. *See Celgene*, 931 F.3d at 1353 ("The fact that there is no long-felt, unmet need does not necessarily mean that there is no motivation to improve a system.").

533. Analysis of whether an invention met a long-felt, unmet need begins at the time a problem is identified and ends at the time of filing of the claimed invention. *See Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem."); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) ("[W]e look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need.").

534. It is not enough for a patentee to identify drawbacks in the prior art; the patentee must "show that these drawbacks constituted a long-felt, unmet need alleviated by the patent." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009).

535. "[O]nce a long-felt need is established, evidence must show that the claimed invention satisfied that need." *In re Gardner*, 449 F. App'x 914, 918 (Fed. Cir. 2011) (citing *In re Cavanaugh*, 436 F.2d 491, 496 (C.C.P.A. 1971)).

536. Even if there is evidence that the "claimed [invention] may have been beneficial," that evidence is not probative if "others had previously solved the long-felt need." *In re PepperBall Techs., Inc.*, 469 F. App'x 878, 882 (Fed. Cir. 2012); *see also Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) ("once another supplied the key element, there was no long-felt need").

537. The inquiry of whether a long-felt need was previously met by the prior art is not limited to products or methods that were commercially available before the priority date. Rather, the previous product or method need only have been "invented or patented before the drug covered by the [asserted] patent." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 684 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014) (quotations omitted).

538. The inquiry of whether a long-felt need was previously met is not limited to products available in the United States, but includes products that were available in other countries. *See AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 388 (D.N.J. 2015), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015) (holding that, before the priority date of the claimed invention, the alleged long-felt "need was satisfied by the nonsterile Pulmicort Respules available in Europe").

539. Similarly, a long-felt need can be previously met by products that are not FDA-approved or commercially available. *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017) (rejecting evidence of long-felt need where the patentee argued that its product "Gilenya [was] the first commercially-available solid oral multiple sclerosis treatment. The treatment of multiple sclerosis with a solid oral composition, however, was indisputably known in the prior art. . . . The fact that Gilenya was the first to receive FDA approval for commercial marketing does not overcome the fact that solid multiple sclerosis compositions were already known.").

540. Evidence of a "long-felt need" is generally not probative in the context of "a niche market," where "it is not surprising that it took a few years for a company to expand on the prior art." *Tokyo Keiso Co. v. SMC Corp.*, 307 F. App'x 446, 453 (Fed. Cir. 2009).

541. "Where the differences between the prior art and the claimed invention are . . . minimal," "it cannot be said that any long-felt need was unsolved." *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

542. "Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

iii. Unexpected results

543. For purposes of unexpected results, "by definition, any superior property must be *unexpected* to be considered as evidence of non-obviousness." *Pfizer*, 480 F.3d at 1371. "[I]n order to properly evaluate whether a superior property was unexpected, the court should . . . consider[] what properties were expected." *Id*.

544. The relevant inquiry is whether the "evidence of unexpected results . . . would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014); *see also id*. at 974 (rejecting patentee's argument that prior-art drug used for obviousness combination "was discovered to be toxic" after the priority date, because at the time it was "not yet known to have high toxicity," and thus the invention's lack of toxicity would not have been unexpected (quotation omitted)).

545. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

546. "Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art." *Galderma*, 737 F.3d at 739 (quotation omitted). Drugs exhibit only "differences in degree" where they generally produce "the same type of biological activity." *In re Merck*, 800 F.2d at 1099. "The fact that [the claimed product and the prior-art product], respectively, helped some patients and not others does not appear significant." *Id*.

547. As with other secondary considerations, "an unexpected result or property does not by itself support a finding of nonobviousness." *Bristol-Myers*, 752 F.3d at 976. The Federal Circuit has

"rejected" the argument that "the existence of unexpected properties forecloses a finding of a reasonable expectation of success." *Id.*; *see also Allergan*, 726 F.3d at 1293 ("We agree with the court's finding that this result was unexpected. However, we do not find that these unexpected results are sufficient to outweigh the other evidence of obviousness as to these formulation claims."); *Richardson-Vicks*, 122 F.3d at 1484 (overturning jury verdict of nonobviousness—"unexpected results . . . , although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious").

548. As with other secondary considerations, a "showing of unexpected results [that] is not commensurate in scope with the degree of protection sought by the claimed subject matter" is not probative of nonobviousness. *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

549. Courts have also held that "for an unexpected property of an invention to be evidence of non-obviousness it must have been contemplated as a goal of the inventive process. The fact that the hypothetical person of ordinary skill would have been surprised to learn that the particular combination of elements created an unexpected benefit completely unrelated to the desired outcome does not logically imply that it would not have been obvious to combine those elements to achieve the desired result." *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 667 (D.N.J. 2006) (rejecting evidence of a drug's "superior cardiovascular properties" that was unrelated to the claimed invention: "The fact that a person of ordinary skill would have been surprised by the cardiovascular properties of Celebrex does not imply that it was not obvious to create this compound to produce an NSAID with reduced gastrointestinal side effects. Thus, this unexpected result does not suggest non-obviousness of the invention and is not relevant to the obviousness inquiry.").

iv. Skepticism

550. The "lack of enthusiasm by a few is not equivalent to skepticism or failure of others such that the combination would not have been obvious to a [skilled artisan]." *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019)

551. When there is "no evidence that [the skeptics] were persons of skill in the relevant art," the evidence does not show industry skepticism. *Warner Chilcott Co. v. Teva Pharm. USA, Inc.,* 89 F. Supp. 3d 641, 671 (D.N.J. 2015), *aff'd*, 642 F. App'x 996 (Fed. Cir. 2016).

552. Statements that experts in the field were "surprised" by the results of the claimed invention are not probative unless those persons "were previously aware of the prior art references that laid the groundwork" for the obviousness challenge. *PharmaStem*, 491 F.3d at 1365 (discounting evidence of "surprise" where there was no indication that the results "would have been surprising to one familiar with the prior art references introduced at trial').

553. As with unexpected results, evidence post-dating the invention is not relevant to skepticism. Rather, the Federal Circuit has only "consider[ed] skepticism or disbelief *before the invention* as an indicator of nonobviousness." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000) (citation omitted; emphasis added); *see also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (noting that "objective evidence of nonobviousness includes . . . skepticism of skilled artisans before the invention"); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (secondary considerations include "[t]he skepticism of an expert, expressed before these inventors proved him wrong").

v. Industry praise

554. "Industry praise must also be linked to the patented invention" in order to be relevant. *Geo. M. Martin*, 618 F.3d at 1305; *see also Paulsen*, 30 F.3d at 1482 (discounting "exceptional praise [from] the industry press," which was "indeed impressive," where the patentee had "not shown that it is relevant to the claims at issue and thus entitled to weight"); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (same—"While the evidence shows that the overall system drew praise as a solution to a felt need, there was no evidence that the success of the commercial embodiment of the [ ] patent was attributable to the . . . material difference between [the prior art] and the patented invention.").

555. "[T]he fact that a drug compound is recommended by treatment guidelines or is prescribed often . . . falls well short of showing true industry praise." *ViiV Healthcare UK Ltd. v. Lupin Ltd.*, 6 F. Supp. 3d 461, 497 (D. Del. 2013).

556. Merely citing "journal citations that reference the findings stated in [the patentee's] published efficacy studies" or the patentee's own "self-referential commendation fall[s] well short of demonstrating true industry praise. Furthermore, industry praise of what was clearly rendered

obvious by published references is not a persuasive secondary consideration." *Bayer*, 713 F.3d at 1377; *see also In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016) (rejecting patentee's reliance on "self-serving statements from researchers about their own work" as alleged evidence of praise); *Geo. M. Martin*, 618 F.3d at 1305 (same—"self-serving statements" are not "industry praise").

557. A statement intended to generate interest in a product also is not evidence of industry praise. *Richardson-Vicks*, 122 F.3d at 1484 n.3 ("This advertisement, according to RVI, represents 'industry acclaim' of the patented invention that constitutes 'strong objective evidence of nonobviousness.' We fail to appreciate the significance of this statement which is intended to generate interest in the product, not prove its superiority.").

558. Praise for a confirmatory clinical trial that proved the claimed invention would work is not relevant where the prior art already provided a reasonable expectation of success. *See PharmaStem*, 491 F.3d at 1365 ("The problem with that evidence is that there was no indication that the praise for the inventors' work was based on any inventive contribution they made, as opposed to their proof, through laboratory work, that fetal blood contains large numbers of stem cells. As noted, the former is a basis for patentability; the latter is not.").

vi. Commercial success

559. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck*, 395 F.3d at 1376. The concept of commercial success is tied "directly to the practical, financial source of impetus for research and development." *Id*. at 1377.

560. As with other secondary considerations, "for commercial success to be probative evidence of nonobviousness, a nexus must be shown between the claimed invention and the evidence of commercial success." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012). Where other "factors [a]re identified as contributing to . . . commercial success, including marketing efforts," such success "does not alter the obviousness analysis." *Id.* If "the evidence does not show that the success of [the] product [i]s directly attributable to [the claimed invention]," the Court must "discount[] the evidence of commercial success as a secondary

consideration rebutting [the] showing that the claimed invention would have been obvious." *Id.* at 1364.

561. Moreover, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) (reversing judgment of nonobviousness); *accord Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) ("If commercial success is due to an element in the prior art, no nexus exists."); *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art").

3. Regulatory exclusivity

562. The reward for a successful study that leads to an approved indication is not patent protection—it is a period of regulatory exclusivity. *See* 21 U.S.C. § 355(j)(5)(F)(iii). "[R]egulatory exclusivity means that FDA [will not] approve any generic product for some particular period" of time. Ketchum Tr. 167:9-14. The purpose of a regulatory exclusivity "is to acknowledge that the sponsor, in arriving at [an] expanded indication[,] has exerted a certain amount of time, energy, and financial where withal to get to that" indication. *Id.*

563. The FDA awards three years of exclusivity when an application contains a new clinical trial, and 5 years when an application contains a new chemical entity ("NCE"). 21 C.F.R. 314.108. The FDA regulations define a "new chemical entity" as "[a] drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 U.S.C. § 355 (j)(5)(F)(iii)-(iv).

4. Bias

564. "[T]he weight given to particular testimony by the [factfinder] can be affected by" the fact that "testifying corporate executives may be biased by a financial interest. Expert witnesses, frequently necessary to explain terminology or the general teachings of the art, may also be similarly biased." *Biodex Corp. v. Loredan Biomedical, Inc.*, 946 F.2d 850, 860 (Fed. Cir. 1991). Considerations of witness bias "are equally applicable to trials of patent issues as to any other," and may affect "the weight given to particular testimony." *Id.*

B. Defendants do not infringe any asserted claim because their labels do not instruct doctors to administer EPA for 12 weeks.

565. All 10 patent claims that Plaintiffs assert against Defendants require administering purified EPA to a patient for at least 12 weeks. DX 1500 ('728 patent claims 1 and 16); DX 1502 ('715 patent claim 14); DX 1504 ('677 patent claims 1 and 8); DX 1506 ('562 patent claim 1); DX 1514 ('560 patent claims 4 and 17); DX 1516 ('929 patent claims 1 and 5). Plaintiffs have failed to prove that Defendants will induce doctors to administer Defendants' products for at least 12 weeks. For this reason alone, Defendants are entitled to judgment of noninfringement as to all asserted claims.

566. As the Court recognized in its Order on Defendants' motion for summary judgment (ECF No. 278), "the question of whether Defendants may be held liable for inducing infringement turns on whether Defendants 'have the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products' in a way that infringes the Asserted Claims. In other words, the Court must ask 'whether the label encourages, recommends, or promotes infringement'" by "'instruct[ing] users to perform the patented method.'" ECF No. 278 at 7 (quoting *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019)).

567. Under this legal standard, the Court found that summary judgment of no inducement was "a close call" because nothing in Defendants' proposed labelling "explicitly tell[s] doctors they should prescribe the drug for at least 12 weeks." *Id*. at 9. At trial, experts for both sides—including Plaintiffs' infringement experts, Drs. Budoff and Peck—confirmed the Court's previous findings. FF ¶¶ 174-179.

568. The Court's summary judgment order left only a narrow window for Plaintiffs to prove inducement: The Court found a triable issue of fact as to whether the indicated use for "severe (≥500 mg/dL) hypertriglyceridemia" "requires" using EPA for at least 12 weeks because "doctors know severe hypertriglyceridemia is a chronic condition requiring indefinite treatment." ECF No. 278 at 9.

569. As shown below, however, Plaintiffs abandoned this theory at trial. Contrary to Plaintiffs' representations to defeat summary judgment, Plaintiffs' experts conceded that severe

hypertriglyceridemia can be acute, and may not require any drug treatment at all, let alone "indefinite treatment."

570. Plaintiffs instead advanced a new theory (which was not set forth in their summary judgment or pretrial briefs) that Defendants' labelling—in particular, the Dosing and Administration section—instructs doctors to rule out all acute causes of severe hypertriglyceridemia before administering EPA, leaving only those patients who actually require long-term drug therapy. Yet this theory, too, was abandoned by Plaintiffs' experts at trial, and is contradicted by Plaintiffs' own MARINE study. In the end, Plaintiffs are left only with the mere description of a 12-week trial in the labelling, which is insufficient to induce infringement as a matter of law.

571. All experts on the issue of infringement agreed that the label as a whole leaves treatment duration to the discretion of the doctor. FF ¶¶ 174-179. Thus, the physician is able to decide, based on the needs of a particular patient, whether to prescribe icosapent for more than or less than 12 weeks. The label expresses no preference for the length of treatment. Because the label does not specify or encourage any particular duration, but rather leaves it up to the physician's discretion, the label does not specifically encourage the patented method of any asserted claim.

1. Plaintiffs failed to prove their original theory that "severe hypertriglyceridemia" necessarily refers to "a chronic condition requiring indefinite treatment."

572. In pursuing their original theory that the indication for "severe hypertriglyceridemia" implicitly requires chronic administration, Plaintiffs faced Federal Circuit precedent holding that when "a product has substantial noninfringing uses, intent to induce infringement cannot be inferred." *HZNP Medicines LLC v. Actavis Labs.*, 940 F.3d 680, 702 (Fed. Cir. 2019) ("*Horizon*") (quotation and alteration omitted). That principle governs this case. As the Court held on summary judgment, "reducing triglycerides in less than 12 weeks using Defendants' ANDA drugs is a substantial non-infringing use of those drugs," including because prescribing EPA "for fewer than 12 weeks is within the scope of the FDA approval reflected in Vascepa's labelling." ECF No. 278 at 12. Thus, induced infringement cannot be found here based on labelling instructions that are merely *inferred*.

573. Instead, under the Court's summary-judgment ruling, Plaintiffs needed to prove that the express instruction in the Indication and Usage section to use Defendants' respective icosapent products to treat severe hypertriglyceridemia necessarily "requir[es]" at least 12-week drug treatment. ECF No. 278 at 12-13. In other words, Plaintiffs had the burden to prove that treating physicians understand that the term "severe hypertriglyceridemia" necessarily refers to a chronic condition requiring long-term drug therapy such as, for example, Multiple Sclerosis or HIV. Absent such proof, the mere fact that the indicated use for treating severe hypertriglyceridemia "includes" chronic use, but does not "specifically encourage" it, is insufficient as a matter of law to show inducement under controlling precedent. *Grunenthal*, 919 F.3d at 1339. Based on undisputed expert testimony from both sides' experts, Plaintiffs were unable to meet their burden.[11]

574. As discussed above, the parties' experts agreed—consistent with the plain language of the Vascepa indication—that severe hypertriglyceridemia simply refers to the fact that a patient's triglycerides are greater than or equal to 500 mg/dL, which can be due to multiple causes. FF ¶¶ 87, 95-100. The purpose of the 500 mg/dL threshold is to assess whether a patient is at risk of pancreatitis, and does not depend on the cause of the triglyceride elevation. FF ¶¶ 86-90, 95. Moreover, many causes of severe hypertriglyceridemia are acute—not chronic. FF ¶¶ 91, 95-100.

575. Indeed, contrary to Plaintiffs' original theory on summary judgment that "severe hypertriglyceridemia is a chronic condition" (ECF No. 278 at 9), Dr. Budoff admitted on cross-examination that severe hypertriglyceridemia is "not always a chronic condition," and instead "can be an acute phenomenon." Budoff Tr. 447:23-25, 449:1-3, 450:12-15; *see also* FF ¶¶ 95-97, 99-100 (listing "reversible causes"). While some patients do have genetic, chronic causes of severe hypertriglyceridemia, Dr. Budoff agreed that "pure genetic disorders" are "rare," and that "the cause of severe hypertriglyceridemia in most patients is not solely genetics." Budoff Tr. 463:1-5, 468:5-11; FF ¶ 98.

[11] During opening statements, Plaintiffs mischaracterized Defendants' pretrial brief as arguing that "the existence of a substantial noninfringing use negates an inducement to infringe." Opening Tr. 23:22-25. That is not Defendants' position. Defendants have consistently argued that inducement "cannot be inferred" from the indicated use unless the label "instructs users to perform the patented method." *Horizon*, 940 F.3d at 702; *see* ECF No. 335 at 13-14. There is no such instruction here.

576. Even apart from these concessions, patients with the principal causes of severe hypertriglyceridemia that are purely genetic—lipoprotein lipase deficiency and Apo C-II deficiency—were excluded from Plaintiffs' MARINE trial, which was the basis for Vascepa's FDA approval and is representative of the population that Vascepa is intended to treat. FF ¶¶ 121, 124-125. Plaintiffs cannot credibly assert that Vascepa is limited to patients with genetic forms of severe hypertriglyceridemia, when such patients were excluded from the clinical trial that led to the drug's approval.

577. Moreover, the FDA recently rejected an attempt by Plaintiffs to characterize patients who take Vascepa as a "chronic care population" in the latest version of Vascepa's label. FF ¶¶ 93-94; *compare* DX 2247 (Vascepa Proposed Label) at 4 *with* DX 2248 (Vascepa Label) at 4. Together with Dr. Budoff's concessions, these facts refute Plaintiffs' contention that severe hypertriglyceridemia is necessarily "a chronic condition."

578. The evidence at trial also refuted Plaintiffs' contention that severe hypertriglyceridemia necessarily "requir[es] indefinite treatment" with a drug. ECF No. 278 at 9. Contrary to Plaintiffs' theory, Dr. Budoff admitted that "a patient with severe hypertriglyceridemia does not necessarily require indefinite drug therapy," and "many patients with severe hypertriglyceridemia don't require any drug therapy at all." Budoff Tr. 489:19-22; 489:23-25. Indeed, Drs. Budoff and Sheinberg agreed that many patients can be treated with lifestyle modifications instead of drug therapy, either to reduce or maintain reductions in triglycerides below the 500 mg/dL threshold. FF ¶¶ 106-108, 111-113.

579. This point was made clear by an article written by Amarin's claim-construction expert, Dr. Miller. For example, the Miller reference teaches that "[p]regnancy (especially in the third trimester)," "[d]rugs (medications)," and "[a]lcohol excess" can cause severe hypertriglyceridemia. DX 1632 (Miller 2011) at 11. Of course, "pregnancy in the third trimester is not a chronic condition." Budoff Tr. 482:8-10. Likewise, several of the drugs listed in Dr. Miller's article that cause severe hypertriglyceridemia "can be taken for less than 12 weeks," such as "steroids . . . [and] interferon." *Id.* at 482:11-21 (Budoff).

580. Dr. Miller also confirmed in his clinical guidance paper that "optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%." DX 1632 (Miller 2011) at 24. Dr. Budoff agreed with this statement. Budoff Tr. 484:16-485:7. Dr. Miller's paper states that "[a] weight loss of 5% to 10% results in a 20% decrease in triglycerides," and a "[m]editerranean-style diet . . . is more commonly associated with an approximately 10% to 15% lowering of triglycerides and a reduced prevalence of hypertriglyceridemia." DX1632 at 20, 22. Again, Dr. Budoff agreed. Budoff Tr. 483:21-484:8.

581. While patients with acute or reversible causes of severe hypertriglyceridemia can reduce their triglycerides with lifestyle modifications, there is no dispute that these patients can still benefit from short courses of EPA drug treatment before their acute causes are resolved, or before lifestyle modifications kick in and take effect. FF ¶¶ 108-113. As the Court previously found, and as the parties confirmed at trial, EPA can reduce triglycerides in severely hypertriglyceridemic patients below 500 mg/dL in just four weeks. ECF No. 278 at 12; FF ¶ 129. The speed with which EPA acts to reduce triglycerides can be critical, because patients with severe hypertriglyceridemia are at risk of pancreatitis—a life-threatening condition. FF ¶¶ 89-90, 110, 134, 155. Dr. Budoff thus agreed that "icosapent works well if a doctor wants a drug to get triglyceride levels below 500 quickly to [reduce] the risk of pancreatitis," and that "a doctor reasonably could prescribe icosapent for short term use to reduce the pancreatitis risk as soon as possible." Budoff Tr. 500:2-13.

582. In fact, 5 percent of Dr. Budoff's own patients take Vascepa for less than 12 weeks. *Id*. at 501:11-14. While the majority of patients end up taking Vascepa long-term, most of those long-term uses are not for the indicated use of reducing triglycerides below 500 mg/dL, but for other purposes, such as reducing long-term cardiovascular risk based on the REDUCE-IT indication (which would be an "off-label" use of Defendants' ANDA products and would not infringe the asserted claims). FF ¶¶ 114-118.

583. In light of these undisputed facts, the Federal Circuit's *Grunenthal* decision from 2019 is on point. In that case, the drug was indicated to treat "severe chronic pain." 919 F.3d at 1339. This indication included, but was not limited to, the patented method of treating a specific type of severe chronic pain—"polyneuropathic pain." *Id*. The patentee argued that the indication would

inevitably lead at least some users to infringe and thus induced infringement implicitly. But the Federal Circuit rejected that theory, holding that "even if severe chronic pain includes polyneuropathic pain, it also includes [other types of severe chronic] pain. Therefore, the proposed ANDA labels do not *specifically encourage* use of [the drug product] for treatment of polyneuropathic pain." *Id*. (emphasis added). There was thus "no induced infringement." *Id*. at 1340.

584. This case presents an analogous situation. Although the indicated use in Defendants' labels for treating severe hypertriglyceridemia "includes" the claimed use of administering EPA for at least 12 weeks, such as for patients suffering from severe hypertriglyceridemia due solely to genetic reasons, "it also includes" shorter durations of drug treatment. *Id*. at 1339. Because the indicated use for treating severe hypertriglyceridemia "do[es] not *specifically* encourage" administering Defendants' products only to those patients who require the drug long-term, there is "no induced infringement." *Id*. at 1339-40 (emphasis added).

585. The frequency of infringing uses does not change the result. In *Grunenthal*, the trial court found that 95% of the drug's uses infringed, but the Federal Circuit still found no induced infringement because the indication did not specifically encourage infringement. *See in re Depomed Patent Litig.*, No. 13-4057(CCC-MF), 2016 WL 7163647, at 69 (D.N.J. Sept. 30, 2016) (finding no inducement where "less than 5%" of uses were noninfringing and 95% of uses infringed), *aff'd sub nom*. *Grunenthal*, 919 F.3d 1333. The facts of this case are remarkably similar to *Grunenthal*. Again, Dr. Budoff confirmed that about 5% of his patients take Vascepa for less than 12 weeks. Budoff Tr. 501:11-14. Regardless of whether the remaining 95% of patients infringe, the indicated use does not specifically encourage such infringement.

586. The Federal Circuit's decision from 2019 in *Horizon* is also instructive. *Horizon* involved a method of treating osteoarthritis of the knee, which required a user to "(1) apply the inventive formulation, (2) wait for the area to dry, and (3) apply sunscreen, insect repellant, or a second topical medication." 940 F.3d at 702. Each step was described in the defendant's label, which instructed users to apply the formulation and then warned to "wait until the treated area is dry before applying a second topical agent, such as sunscreen, insect repellant, or covering the area with clothing." *Id*. at 686 (quotation and alteration omitted). "The district court held that this warning

was insufficient to show induced infringement because [the] claimed method *requires* application of a second topical agent whereas the label *merely permits*, without encouraging, post-product application of sunscreen, insect repellant, or a second topical medication." *Id*. The Federal Circuit affirmed. Citing *Takeda*, it reaffirmed that "[m]erely describing the infringing use, or knowing of the possibility of infringement, will not suffice; specific intent and action to induce infringement must be shown." *Id*. at 702 (citing *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015)). Applying this principle, the *Horizon* court that "[t]he patented method here *requires* three distinct steps," whereas the accused drug label "only *require*[*s*] the first step of this method." *Id*. at 702 (emphasis added). Because "the label does not *require* subsequent application of sunscreen," as required by the asserted claims, the label "does not encourage infringement." *Id*. (emphasis added).

587. In reaching this conclusion, the Federal Circuit rejected the patentee's arguments that inducement should be found merely because the "labeling tracks closely with the asserted claims" and thus "will lead to an infringing use" in at least some cases. *Id*. at 701. The Federal Circuit explained that "[t]he fact that [the defendant's] label does not require subsequent application of other products reflects that the product has 'substantial noninfringing uses, [and] intent to induce infringement cannot be inferred.'" *Id*. at 702 (quoting *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003) (alteration in original)). Although the patentee's evidence "establishe[d] that some users might infringe," in light of the product's substantial noninfringing uses, that evidence could "not establish that 'the proposed label *instructs* users to perform the patented method.'" *Id*. (emphasis added).

588. Again, a similar analysis applies to this case. Even though the indicated use to treat severe hypertriglyceridemia *permits* long-term treatment, it does not "require" such treatment. *Id*. at 702. Particularly since Defendants' products have substantial noninfringing uses, the mere fact that some or even many patients will require long-term treatment is not enough to "infer" that Defendants have the specific intent to induce infringement. *Id*.[12]

[12] At the summary judgment stage, where all factual inference had to be drawn in Plaintiffs' favor, the Court distinguished *Horizon* because "Plaintiffs' expert testimony offers a plausible interpretation

589. At the summary judgment stage, Plaintiffs relied heavily on *Sanofi v. Glenmark Pharm. Inc., USA*, 204 F. Supp. 3d 665 (D. Del. 2016) ("*Sanofi I*"), where the District of Delaware found induced infringement of a claim that required treating a patient with the claimed drug "for at least 12 months." *Id*. at 683. The drug was indicated for treating atrial fibrillation, and "[b]oth parties' experts . . . testified that atrial fibrillation is a chronic disorder." *Id*. at 683. By contrast, as discussed above, both parties' experts in this case testified that, for many patients, severe hypertriglyceridemia is not a chronic disorder—and can even be an acute phenomenon. For this reason alone, *Sanofi I* is distinguishable.

590. In any event, *Sanofi I* is not controlling, and preceded the Federal Circuit's rulings in both *Grunenthal* and *Horizon*. The district court's holding regarding the duration of treatment applied to only one claim, was not appealed, and thus was never considered by the Federal Circuit. *See Sanofi v. Watson Labs. Inc*., 875 F.3d 636 (Fed. Cir. 2017) ("*Sanofi II*"). The district court in *Sanofi I* also relied on explicit "safety and monitoring information" in the labels, "which suggest[ed] that the drug is intended for long-term use." *Id*. at 683-84. Here, as discussed above and in greater depth below, there are no explicit statements or other suggestions regarding—much less instructions requiring—long-term use in Defendants' labels. *Sanofi I* is thus inapposite and does not support Plaintiffs.

591. In sum, Plaintiffs failed to meet their burden of proving that "doctors know severe hypertriglyceridemia is a chronic condition requiring indefinite treatment." ECF No. 278 at 9. On the contrary, both sides' experts agreed that severe hypertriglyceridemia does not "requir[e] indefinite treatment," because it is often not chronic and can often be treated with lifestyle modifications alone, or with short-term drug therapy combined with lifestyle modifications. *Id*. Thus, the theory of infringement that Plaintiffs presented on summary judgment is not supported by a preponderance of the evidence, and does not warrant a finding of inducement.

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of the labelling that suggests the Court could find induced infringement." ECF No. 278 at 10 n.4. In particular, Plaintiffs alleged that "doctors know severe hypertriglyceridemia is a chronic condition requiring indefinite treatment." *Id*. at 9. As discussed, however, based on all the evidence at trial, Plaintiffs have failed to meet their burden of supporting this theory of infringement.

2. Plaintiffs failed to prove their new theory that the Dosage and Administration section will inevitably lead doctors to administer EPA only to patients who require long-term drug treatment.

592. Lacking support for their original theory of infringement, Plaintiffs and Dr. Budoff presented a new theory at trial for why Defendants' labels induce infringement—a theory that Plaintiffs did not raise in their summary judgment or pretrial briefs. This new theory relies on Section 2.1 of the labelling, which is in the Dosage and Administration section and reads as follows:

> **2 DOSAGE AND ADMINISTRATION**
>
> **2.1 Prior to Initiation of Icosapent Ethyl**
>
> - Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate.
> - Patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl, which should continue during treatment with icosapent ethyl.

DX 2256 (Hikma Label) at 2; DX 2266 (DRL Label) at 2.

593. According to Plaintiffs' new theory, both of the bulleted statements in Section 2.1 will inevitably lead at least some doctors to infringe. Plaintiffs contend that the statement, "Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate," will lead doctors to eliminate acute or reversible causes of severe hypertriglyceridemia before administering EPA. Similarly, Plaintiffs contend that the statement, "Patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl," will lead doctors to treat their patients with diet and exercise first, and forego the administration of EPA unless and until diet and exercise have failed. According to Plaintiffs, while neither of these bulleted statements explicitly tells doctors to administer EPA for at least 12 weeks, that is the inevitable result of following their guidance. That is, Plaintiffs contend that the language in Section 2.1 effectively instructs doctors to rule out any acute, reversible causes of severe hypertriglyceridemia that can be treated with lifestyle modifications, thus reserving EPA only for

patients who have chronic forms of severe hypertriglyceridemia that require indefinite treatment. 52(c) Mot. Tr. 621:22-622-17.

594. As discussed below, however, Plaintiffs did not meet their burden of proving this theory at trial. First, the case law that Plaintiffs rely on makes clear that, for inevitable inducement, it is not enough that some physicians following the label will end up infringing. The label must include an express instruction that actually leads to infringement. Second, FDA guidance and regulations make clear that any instruction that limits the indicated patient population (in this case, by eliminating patients with acute causes of severe hypertriglyceridemia) would need to be in the Indications and Usage section. Here, it is not. Third, the language that Plaintiffs rely on in the Dosage and Administration section does not actually instruct doctors to rule out acute causes of severe hypertriglyceridemia, or even to pretreat patients with diet and exercise. Even if it did, the results of the MARINE study show that pretreatment with diet and exercise will not eliminate all patients with non-chronic forms of severe hypertriglyceridemia. Plaintiffs' new theory of infringement thus fails for multiple reasons.

a. To show inevitable inducement, Plaintiffs must point to an instruction in the label that actually leads to infringement.

595. As support for their new infringement theory, Plaintiffs rely heavily on the Federal Circuit's decisions in *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010), and *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357 (Fed. Cir. 2017), both of which addressed whether a defendant's label would inevitably lead some doctors to infringe. Both cases are clear that to make this showing, the plaintiff must prove that the label contains an actual instruction to doctors, and that following a specific instruction would inevitably—i.e., necessarily—result in infringement.

596. *AstraZeneca* did not involve an actual finding of infringement, but merely affirmed the grant of a preliminary injunction under the clear-error standard. 633 F.3d at 1061.[13] The dispute centered on whether the defendant's label would induce doctors to administer an asthma medication

[13] Similarly, the Court previously distinguished *Takeda*, 785 F.3d 625, on the basis that it "arose in a different procedural context [(i.e. the preliminary injunction context)], where a different legal standard governed the court's analysis." ECF No. 278 at 11 n.5.

"once daily," as required by the patented method. *Id*. at 1057. The drug was "available in only two strengths: 0.25 mg and 0.5 mg per 2 mL vial," each of which "must immediately be administered in its entirety because dividing the contents of a vial for use at different times would compromise the drug's sterility." *Id*. The Dosage and Administration section of the label included a table with the "total daily dose" for three groups of patients, which was "0.5 mg total daily administered twice daily in divided doses" for the first two groups—i.e., two doses of 0.25 mg. *Id*. The same section further stated that "[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved," and that "[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose." *Id*. Based on the starting dose of 0.25 mg twice daily, and the instruction to "downward-titrate" that dose after the patient's asthma was stabilized, the district court "reasoned that the first step in titrating down from this dose would have to be 0.25 mg once daily, as there was no way of decreasing the amount of each dose below 0.25 mg." *Id*. In other words, for patients who "fell within the first two rows of the dosage table, the downward-titration language would *necessarily lead* patients to use a 0.25 mg vial of the drug once-daily." *Id*. (emphasis added). The district court thus found it likely that the plaintiff would be able to show inducement at trial. *Id*.

597. In affirming the preliminary injunction, the Federal Circuit made clear that "[t]he pertinent question is whether the proposed label instructs users to perform the patented method." *Id*. at 1060. Based on that standard, the Federal Circuit found that the district court did not clearly err in finding that the plaintiff was likely to prove that "the downward-titration language" in the label "would inevitably lead some consumers to practice the claimed method." *Id*. That is, based on the indicated starting doses and the explicit instruction to titrate the dose downwards, the Federal Circuit was "not left with a definite and firm conviction that a mistake ha[d] been made" in finding that the labelling would likely encourage once-daily administration. *Id*. The case then settled and, thus, there was no ultimate decision on the merits of the induced-infringement claim in that case—by the district court, or the Federal Circuit.

598. In applying and interpreting—and, often, distinguishing—*AstraZeneca*, courts have been consistent in noting that the decision involved an explicit instruction to doctors that inevitably

resulted in infringement. *See Otsuka Pharm. Co. v. Torrent Pharm. Ltd., Inc.*, 99 F. Supp. 3d 461, 495 n.29 (D.N.J. 2015) (citing 633 F.3d at 1057-59) ("Critically, in affirming the district court's grant of a preliminary injunction, the *AstraZeneca* court relied upon the fact that the generic's label contained *explicit* instructions in the 'Dosage and Administration' section to administer the product in an infringing manner."); *Takeda Pharm. USA, Inc. v. W.-Ward Pharm. Corp.*, 72 F. Supp. 3d 539, 544 (D. Del. 2014) (in *AstraZeneca*, "the district court found more in the label than an 'implicit' instruction," and the Federal Circuit, "for its part," merely affirmed under the deferential clear-error standard—"[n]ot exactly a ringing endorsement of the decision to enjoin Apotex"); *see also In re Depomed Patent Litig.*, 2016 WL 7163647, at *64, *aff'd sub nom. Grunenthal*, 919 F.3d 1333 (distinguishing *AstraZeneca* and noting that the relevant question is whether the "label 'includes instructions . . . that will *cause*' those users to infringe'") (quoting 633 F.3d at 1060 (alteration and emphasis in original)); *Horizon*, 940 F.3d at 702 (distinguishing *AstraZeneca* where "[t]he evidence . . . [did] not establish that 'the prosed label *instructs* users to perform the patented method") (emphasis added); *Grunenthal*, 919 F.3d at 1340 (distinguishing *AstraZeneca* because the defendants' labels did "not implicitly or explicitly encourage or instruct users to take action that would inevitably lead to" infringing use).

599. *Eli Lilly* similarly focused on whether explicit instructions in the label would inevitably lead to infringement. In that case, the patented method required administering folic acid before administering Alimta (pemetrexed), a chemotherapy drug. 845 F.3d at 1361. The label for generic pemetrexed stated: "Instruct patients to initiate folic acid . . . once daily beginning 7 days before the first dose of [pemetrexed]." *Id*. at 1364 (alteration in original). Based on this and other statements, the Federal Circuit found that "the product labeling includes repeated instructions and warnings regarding the importance of and reasons for folic acid treatment," and that "[t]he instructions are unambiguous on their face and encourage or recommend infringement." *Id*. at 1369. The court thus found that "the product labeling that Defendants seek would inevitably lead some physicians to infringe" by administering folic acid to their patients before administering pemetrexed. *Id*.

600. In both *AstraZeneca* and *Eli Lilly*, therefore, the issue of inevitable inducement turned on (1) whether the labelling set forth a relevant instruction that was directed to at least some doctors or patients; and (2) whether following that specific and express instruction would inevitably lead to infringing the claims. The Federal Circuit has consistently held that, without such an instruction, "[s]peculation or even proof that some, or even many, doctors would [infringe] is hardly evidence of inevitability." *Takeda*, 785 F.3d at 631, 633. Here, as discussed below, Plaintiffs have not met their burden of showing that there is any relevant instruction, let alone one that would inevitably lead to infringement.

b. If the approved use of EPA were limited to chronic patients, that limitation would need to be in the indication—and it is not.

601. As an initial matter, Plaintiffs' theory that the *Dosage and Administration* section limits the use of EPA to patients with chronic forms of severe hypertriglyceridemia or to patients who have previously tried diet and exercise is contrary to FDA regulations and guidance, which make clear that any such limitation must be in the *Indications and Usage* section.

602. The FDA's "guidance for industry" states that the "Indications and Usage" section must set forth the "[s]elected patient subgroups or disease subpopulations for whom the drug is approved." PX 573 at 11. In other words, "the indication should clearly convey the patient population for which the drug is approved." *Id*. If the drug's use is limited to "patients previously treated with other therapies," for example, that limitation must be in the indication. *Id*. Plaintiffs' regulatory expert, Dr. Peck, testified that this guidance is authoritative. FF ¶ 141.

603. Based on the FDA's industry guidance, it is clear that the labelling here does not require doctors to rule out acute causes of severe hypertriglyceridemia, or to try reducing triglycerides below 500 mg/dL with diet and exercise, before administering EPA. If Vascepa or Defendants' drug products were limited to treating patients with chronic forms of severe hypertriglyceridemia—i.e., "[s]elected patient subgroups or disease subpopulations"—that limitation would need to be "clearly convey[ed]" in the Indications and Usage section. PX 573 at 11. Likewise, if the drug were limited to treating "patients previously treated with other therapies," such as diet and exercise, that limitation would also need to be stated in the Indications and Usage section. *Id*.

604. Along the same lines, FDA regulations make clear that the "[i]ndications and usage" section "must include" any "specific tests [that] are necessary for selection or monitoring of the patients who need the drug," as well as any "specific conditions that should be met before the drug is used on a long term basis." 21 C.F.R. § 201.57(c)(2)(i)(C), (F). Like the industry guidance, the regulations make clear that the labels here do not require doctors to rule out acute causes of severe hypertriglyceridemia, or attempt to treat the condition with lifestyle modifications, before administering EPA. Again, any such "specific tests" or "specific conditions" for selecting "the patients who need the drug" would need to be set forth in the Indications and Usage section. *Id*. The Indications and Usage section of Defendants' labels, however, includes no such limitations. As discussed above, the term "severe hypertriglyceridemia" itself does not imply a chronic condition, because it refers to both chronic and acute causes of having triglycerides of at least 500 mg/dL. Nor is there any instruction or suggestion in the Indications and Usage section that the drug should be administered solely to patients who require the drug indefinitely. FF ¶¶ 145-158.

605. None of this is seriously disputed. As Dr. Peck admitted, "the indicated use of icosapent in defendants' labels is not limited to chronic use." Peck Tr. 1361:8-10. Moreover, the FDA rejected the characterization of Vascepa patients as a "chronic care population." FF ¶¶ 93-94. As Dr. Peck conceded, "whether a physician prescribes Vascepa for 12 weeks, 24 weeks or even just three weeks, any such use would be within the scope of FDA's approval." Peck Tr. 1395:11-13. "[I]n other words, because FDA approved Vascepa without specifying any minimum or maximum duration of use, use for any period of time is consistent with the labeling." *Id*. at 1395:13-17 (Peck). Thus, "a doctor could even prescribe icosapent for only three weeks and it would not be inconsistent with the label." *Id*. at 1403:11-13 (Peck). Nor is there any suggestion that the use of EPA is limited to patients who have previously tried to modify their diet. As Dr. Peck admitted, "if FDA had intended to limit Vascepa's approval to patients who previously consumed a particular diet, it would have so stated in the Indications and Usage section. The absence of any such limitation thus conveys to physicians that the approved patient population is bounded by only two characteristics, age and disease condition." *Id.* at 1373:2-8 (Peck).

606. These admissions are dispositive. Because the Indications and Usage section does not limit the use of Vascepa or Defendants' products to patients who require the drug long-term, or who have previously failed attempts at diet and exercise, Plaintiffs' theory that the label limits the use of the drug to patients with chronic forms of severe hypertriglyceridemia fails.

c. The Dosage and Administration section does not instruct doctors to rule out acute causes of severe hypertriglyceridemia.

607. Even apart from its inconsistency with FDA requirements, Plaintiffs' infringement theory based on the Dosage and Administration section was contradicted at trial by Plaintiffs' own witnesses. Based on their admissions, the statements that Plaintiffs point to in Section 2.1 do not instruct doctors in the way that Plaintiffs contend, and would not inevitably lead to infringement.

608. As to the first bullet in Section 2.1, Plaintiffs failed to prove that the statement, "Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate," instructs doctors to eliminate acute or reversible causes of severe hypertriglyceridemia before administering EPA. On its face, the statement instructs no such thing. It merely tells doctors to "manage as appropriate" certain factors that could contribute to elevated triglycerides—with no regard to whether, when, or to whom EPA should be administered.

609. As Dr. Budoff admitted, "if doctors identify other causes, the label leaves it up to the discretion of the doctor to manage as the doctor feels is appropriate." Budoff Tr. 470:7-10. Contrary to Plaintiffs' theory, Dr. Budoff agreed that "in this first bullet, the label is not telling doctors don't give icosapent yet, address those other factors first." *Id*. at 470:11-14 (Budoff). Dr. Budoff further conceded that the statement "certainly isn't saying only give icosapent if absolutely necessary and the only causes are genetics." *Id*. at 470:15-18 (Budoff). As discussed above, additional testimony from both sides' experts confirms that the first bullet in Section 2.1 does not instruct doctors to rule out acute causes of severe hypertriglyceridemia before administering EPA, or limit EPA to chronic patients. FF ¶¶ 149-158. In short, as with Plaintiffs' theory of infringement on summary judgment, Plaintiffs' experts abandoned Plaintiffs' theory based on the first bullet of Section 2.1.

610. As to the second bullet in Section 2.1, Plaintiffs failed to prove that the statement, "Patients should engage in appropriate nutritional intake and physical activity before receiving

icosapent ethyl," instructs doctors to withhold EPA until patients have completed pretreatment with diet and exercise—let alone that such pretreatment will inevitably exclude patients with acute forms of severe hypertriglyceridemia, leaving only those patients who require chronic drug therapy.

611. First, while Dr. Budoff contended that the label instructs doctors to try diet and exercise before they administer EPA, his own testimony substantially undermined that theory. As Dr. Budoff admitted, patients with triglycerides above 500 mg/dL are at risk of pancreatitis, which "can be a life-threatening condition." Budoff Tr. 480:13-16, 473:18-20. Treatment guidelines thus "advise that clinicians immediately treat severely hypertriglyceridemic patients with triglyceride lowering drugs." *Id*. at 479:12-22 (Budoff); *see also* FF ¶¶ 155-157. Yet, according to Dr. Budoff, Section 2.1 of the label instructs the opposite, and requires doctors to withhold drug therapy until diet and exercise have failed. This is despite Dr. Budoff's belief that lifestyle modification "doesn't usually work" and that "most patients fail diet and exercise as a primary treatment strategy." Budoff Tr. 491:22-24, 540:13-14. This is not a credible reading of the labelling. It is implausible that the FDA would require doctors to withhold drug therapy in favor of a first-line approach that "most patients . . . fail," when the condition being treated is widely recognized as a medical emergency that is "life-threatening." *See also* ECF No. 327 at 12 (Plaintiffs' trial brief stating that "[s]evere hypertriglyceridemia is *life-threatening* because it puts patients at risk of acute pancreatitis").

612. Second, Dr. Budoff's reading of Section 2.1 was directly contradicted by Plaintiffs' own expert on FDA labelling, Dr. Peck. As discussed above, Dr. Peck conceded that if the use of EPA were limited to patients who had previously engaged in diet modifications, that limitation would need to be clearly stated in the Indications and Usage section. But even putting that aside, Dr. Peck admitted that the labelling otherwise "does not limit the patient population for whom Vascepa is approved based on prior diet," and "does not suggest that Vascepa should be withheld until a patient has successfully effected a change in diet." Peck Tr. 1367:16-18, 1375:20-22. In particular, Dr. Peck agreed that Section 2.1 "does not require doctors to wait and see if patients fail to maintain triglycerides below 500 [mg/dL] with diet and exercise before prescribing icosapent." *Id*. at 1381:13-17 (Peck). And, Dr. Peck admitted that "the labeling does not suggest in any section that the drug

should not be used . . . unless a patient has been placed successfully on a diet for a specific amount of time." *Id*. at 1382:22-25 (Peck).

613. To be sure, Section 2.1 states that "[p]atients should engage in appropriate nutritional intake and physical activity *before* receiving icosapent ethyl," but all experts agreed that there is no specified time period "before" which a doctor can administer EPA. FF ¶¶ 153-157. As Dr. Sheinberg explained, moreover, "engaging in appropriate nutritional intake" within the meaning of Section 2.1 "include[s] *restraining* from eating certain foods," which begins as soon as the patient consults with the physician. Sheinberg Tr. 608: 21-609:10.

614. Dr. Peck also agreed that the word "should" in Section 2.1 indicates that pretreatment with diet and exercise "is not a requirement," because the language "leaves discretion" to physicians on how and when to begin drug therapy. Peck Tr. 1380:8-12. This is in stark contrast to the label for Alimta (pemetrexed) at issue in *Eli Lilly*, which expressly mandated pretreatment for a fixed duration of time: "Instruct patients to initiate folic acid . . . once daily beginning 7 days before the first dose of [pemetrexed]." 845 F.3d at 1364 (alteration in original); Peck Tr. 1388:6-11. Here, unlike in *Eli Lilly*, the labelling mandates neither any specific type of pretreatment, nor any specific duration of pretreatment. Thus, in Dr. Peck's words, Section 2.1 "does not prevent physicians from, consistent with established clinical practice, discussing diet changes and prescribing Vascepa in the same visit." Peck Tr. 1380:23-1381:2. This comports with the clinical reality that diet modifications often involve *ceasing* conduct, such as stopping the intake of excess alcohol or sugars. FF ¶¶ 104, 152-154. These modifications occur immediately after a doctor counsels a patient, and can begin in the same visit that a doctor prescribes EPA. *Id*.

615. While Dr. Budoff disagreed with Dr. Peck on whether the label is limited to chronic use, Dr. Budoff conceded that he is not qualified as an expert in FDA labelling. Budoff Tr. 452:15-18. In fact, Dr. Peck's testimony from the perspective of an FDA regulatory expert was unrebutted at trial. Moreover, it is worth noting that the two experts who disagreed with Dr. Budoff on the meaning of Section 2.1—Dr. Peck and Dr. Sheinberg—had no previous affiliation with any party in the case. By contrast, Dr. Budoff is admittedly affiliated with Plaintiffs outside this case, and has received substantial compensation from Plaintiffs as a paid speaker for Vascepa. FF ¶ 45.

Particularly when deciding which witness is more credible on a particular issue, evidence that an expert is "biased by a financial interest" to favor a party's position may affect "the weight given to particular testimony." *Biodex Corp. v. Loredan Biomedical, Inc.*, 946 F.2d 850, 860 (Fed. Cir. 1991).

616. Third, even if the label could be read as implicitly instructing doctors to try diet and exercise first for a substantial period of time before administering EPA (it certainly does not say this expressly), uncontested evidence from Plaintiffs' own MARINE study shows that such an instruction would not inevitably lead to infringement.

617. As shown by the clinical study protocol for MARINE, and explained by both Dr. Budoff and Dr. Sheinberg at trial, all patients in MARINE were initially treated with diet and exercise alone for 4-6 weeks, followed by a 2-3 week qualifying period to ensure that they had severe hypertriglyceridemia when the 12-week trial began. FF ¶ 123. At that point, patients were divided into treatment groups who received Vascepa and a placebo group, who did not receive Vascepa but continued engaging in diet and exercise for 12 weeks. FF ¶ 127. There is no dispute that Vascepa and Defendants' products are indicated to treat all of the patients who qualified for MARINE after diet and exercise, including the patients in the placebo arm of the study. FF ¶¶ 121, 123, 133.

618. Under Plaintiffs' and Dr. Budoff's theory that engaging in diet and exercise before receiving EPA will eliminate patients with acute causes of severe hypertriglyceridemia, all of the patients who qualified for MARINE would have chronic forms of the condition that necessarily persist without indefinite drug therapy. Yet the results of MARINE show otherwise. As explained in the FDA's medical review for Vascepa, 21% of patients in the placebo arm—i.e., 21% of patients who qualified for the study after engaging in an extended period of diet and exercise, but who did not receive EPA—were able to reduce their triglycerides below 500 mg/dL without any drug therapy, simply by continuing with diet and exercise. FF ¶¶ 132-134; DX 1701 at 51.

619. In other words, at least one-fifth of patients in the placebo arm, who are undisputedly patients whom Vascepa is indicated to treat, Budoff Tr. 493:3-494:3, 494:13-495:10, did *not* have a chronic form of severe hypertriglyceridemia that requires indefinite drug treatment. Thus, even assuming that Plaintiffs and Dr. Budoff are correct that Section 2.1 requires pretreating patients with

diet and exercise before receiving EPA, that pretreatment would not eliminate all patients with acute or reversible forms of severe hypertriglyceridemia.

620. Dr. Budoff agreed, moreover, that if the 21% of patients in the placebo group "were given Vascepa immediately" instead of going through an initial period of diet and exercise, "their triglyceride levels would drop more quickly" below 500 mg/dL. Budoff Tr. 495:20-23. He further agreed that "by the time you get into the 12-week period, they wouldn't even need Vascepa, according to MARINE, to maintain levels above 500." *Id*. at 495:24-496:4 (Budoff). This is exactly how Defendants have contended that EPA can be used short-term. As confirmed by MARINE and Dr. Budoff's testimony, EPA can be given to patients for less than 12 weeks to quickly reduce their triglycerides below 500 mg/dL (thereby reducing their risk of pancreatitis), and those patients can then stop taking EPA and maintain their triglyceride reductions with diet and exercise alone. Again, this is consistent with the labelling, including Section 2.1.

621. As Dr. Budoff conceded, "putting aside all of [his] testimony with regard to the [D]osage and [A]dministration section . . . it would be consistent with the Vascepa labeling and thus defendants' labels for a doctor to prescribe icosapent ethyl for fewer than 12 weeks." *Id*. at 480:17-22 (Budoff). This is consistent with additional admissions by Dr. Budoff and Dr. Peck:

- "[T]he Vascepa label, as well as defendants' labels, leave it entirely up to the physician's discretion to determine the duration of treatment." Budoff Tr. 444:8-1.
- "[D]efendants' labels will allow doctors to tailor treatment duration to the individual patients." Budoff Tr. 444:12-16.
- "The doctor has discretion to use the drug for as long as he thinks is in the best interest of the patient absent a limitation." Peck Tr. 1406:12-21.
- "[I]t would be entirely consistent with defendants' labels for a doctor to prescribe icosapent for less than 12 weeks." Budoff Tr. 445:5-8.
- "[T]o be clear, there's no statement anywhere in defendants' labels requiring doctors to use icosapent for at least 12 weeks." Peck Tr. 1390:1-4.

622. Accordingly, Plaintiffs have failed to prove that the Dosage and Administration section of Defendants' labels would inevitably lead doctors to infringe.

3. At most, the labelling merely describes a 12-week clinical study, which is insufficient to induce infringement as a matter of law.

623. Ultimately, Plaintiffs are left only with the fact that the labelling describes a clinical study that lasted 12 weeks. This description is mainly in the Clinical Studies section of the label, which the parties focused on at trial, although the fact that the trial lasted 12 weeks is also repeated in the adverse reactions and clinical pharmacology sections. FF ¶¶ 161, 167. In total, the 12-week duration appears three times in the labelling. Each instance is reproduced below:

- "In two randomized, double-blind, placebo-controlled trials in patients with triglyceride levels between 200 and 2000 mg/dL treated for 12 weeks, adverse reactions reported with icosapent ethyl at an incidence ≥1% more frequent than placebo based on pooled data included arthralgia and oropharyngeal pain."
- "In a 12-week, dose-ranging study in patients with severe hypertriglyceridemia, icosapent ethyl 4 grams per day reduced median TG from baseline relative to placebo *[see Clinical Studies (14)]*."
- "The effects of icosapent ethyl 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on icosapent ethyl, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks."

DX 2256 (Hikma Label) at 3, 5, 7; DX 2266 (DRL Label) at 3, 6, 8.

624. None of these statements can be interpreted as an instruction to administer EPA for at least 12 weeks. On their face, each statement merely describes the fact that a clinical study was conducted and happened to last 12 weeks. As the Court previously found on summary judgment, "the [C]linical [S]tudies section of the labelling describes a clinical trial (the 'MARINE Trial') in which patients were enrolled for 12 weeks," but this description does not "explicitly tell doctors they should prescribe the drug for at least 12 weeks." ECF No. 278 at 9. The same is true for the new statements in the revised labelling that also describe a 12-week trial. Indeed, Plaintiffs' experts did not cite these new statements at trial or suggest that any different analysis applies to them.

625. Although Plaintiffs' experts offered the conclusory opinion that the Clinical Studies section of the label somehow encourages doctors to administer the drug for at least 12 weeks, they were forced to admit on cross-examination that this section provides merely a description of that

duration. *See* FF ¶¶ 159-163. As Dr. Budoff admitted, "[t]he only time the term 12 weeks is used in defendants' label is to describe the underlying clinical trial." Budoff Tr. 504:4-8. He agreed, moreover, that the language does not "otherwise comment on the 12-week duration such as saying because these effects were achieved in 12 weeks, make sure you give the drug for at least 12 weeks." *Id*. at 504:9-13 (Budoff). In fact, Dr. Budoff conceded that a doctor would not necessarily expect any of the effects described in the Clinical Studies section—in a 12-week period or otherwise—because the reported "median data from a clinical trial may or may not relate to an individual patient" being treated. *Id*. at 512:6-9 (Budoff); FF ¶¶ 160-166. In this respect, Dr. Peck's testimony was consistent with Dr. Budoff's. He agreed that "there's no statement anywhere in defendants' labels requiring doctors to use icosapent for at least 12 weeks," and the labels "never say that icosapent is safe and effective only if administered for at least 12 weeks." Peck Tr. 1390:21-24. At most, "the labeling is telling doctors that they can use the drug for 12 weeks or longer if they want, but it's not saying that they should." *Id*. at 1397:1-6 (Peck).

626. Additionally, doctors know that the actual use of the drug can be shorter or longer than the clinical study. Some drug labels, for example, describe more than one duration in the Clinical Studies section. For example, the Clinical Studies section of the Lovaza label describes one trial that lasted six weeks, and another trial that lasted 16 weeks. DX 1578 (Lovaza Label) at 1.

627. As a matter of law, this is not enough to prove that Defendants have the specific intent to induce infringement with respect to the claimed 12-week duration. "*Merely describing the infringing use*, or knowing of the possibility of infringement, *will not suffice*; specific intent and action to induce infringement must be shown." *Horizon*, 940 F.3d at 702 (emphasis added). Like the conditional statements in *Horizon*, the statements about a 12-week duration here merely describe an infringing use. Merely describing the duration of a clinical trial "does not require" using the drug for the same period of time, and thus "does not encourage infringement." *Id*.

628. Moreover, the evidence at trial showed that when the FDA intends a particular treatment duration for a drug, that duration is stated in the Indications and Usage or Dosage and Administration sections—not in the Clinical Studies section. FF ¶¶ 146-147, 159, 166; DX 1984 (Lamisil Label) at 2 (instructing "12 weeks" duration in Dosage and Administration section); DX

1679 (Lovenox Label) at 5 (instructing "a minimum of 5 days" duration until anticoagulant effect is achieved). These examples are consistent with FDA regulations and guidance, which provide that the "clinical studies" section "must not imply or suggest indications or uses or dosing regimens not stated in the 'Indications and Usage' or 'Dosage and Administration' section." 21 C.F.R. § 201.57(c)(15)(i); DX 1681 (FDA Guidance on Clinical Studies section) at 6. As discussed above, there is no dispute that the claimed use of EPA for at least 12 weeks is not stated in the Indications and Usage or Dosage and Administration sections, which are silent about the duration of drug treatment. FF ¶¶ 136-158. All experts at trial agreed that those sections—and indeed, the labels as a whole—leave the duration of treatment "entirely up to the physician's discretion." FF ¶¶ 136-158, 174-176.

629. Plaintiffs rely on the Federal Circuit's decision in *Sanofi* as precedent for finding inducement based on a clinical trial described in the labelling, but that case is inapposite. In *Sanofi*, the Indications and Usage section expressly referenced the Clinical Studies section. *Sanofi II*, 875 F.3d at 643. Specifically, the Indications and Usage section "sa[id] that [the drug] is indicated for use in certain patients and *refer*[*red*] *to section 14 on 'Clinical Studies'* for identification of those patients." *Id*. (emphasis added). This explicit reference in the Indications and Usage section was critical to the outcome. As the Federal Circuit explained in *Sanofi II*: "The reference to the Clinical Studies section [ ] of the label *expressly directs* the reader to that section for elaboration of the class of patients for whom the drug is indicated." *Id*. at 645 (emphasis added). Likewise, the district court in *Sanofi I* found that "the Indications and Usage section" contained a "*directive* [to] review … the [C]linical [S]tudies section," thus "*direct*[*ing*] a physician to look at" it. 204 F. Supp. 3d at 679, 674 (emphasis added). There is no such reference or "directive" in this case. The Indications and Usage section of Defendants' labels does not mention the Clinical Studies section at all, let alone "expressly direct[] the reader to that section for elaboration" on how long to administer the drug. *Sanofi II*, 875 F.3d at 645.

630. Plaintiffs also rely on *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International*, where the Federal Circuit relied in part on the pharmacokinetics section to find inducement. 887 F.3d 1117, 1131 (Fed. Cir. 2018). Although the court in *Vanda* did not rely on the

Clinical Studies section, Plaintiffs argue that *Vanda* shows that it is appropriate to look beyond the indications and uses or Dosage and Administration sections to other sections of the label that describe the effects of the drug. Similar to the Indications and Usage section in *Sanofi*, however, the Dosage and Administration section in *Vanda* expressly referred to the pharmacokinetics section, and the Federal Circuit expressly cited this reference before relying on the pharmacokinetics section. *See id.* at 1131 (quoting "Dosage and Administration" section, which stated: "Iloperidone dose should be reduced by one-half for poor metabolizers of CYP2D6 [*see Pharmacokinetics (12.3)*]" (emphasis omitted)). Again, there is no cross-reference here from the Dosage and Administration section to the Clinical Studies section. In fact, there is no suggestion anywhere in the label that a doctor should look to the Clinical Studies section to determine the duration of drug therapy.

631. Plaintiffs have also cited *Vanda* for the proposition that expert testimony can establish how clinicians interpret terms in a label. ECF No. 331 ¶ 298. As discussed above, however, the expert testimony in this case failed to establish that doctors interpret "severe hypertriglyceridemia" as necessarily referring to a chronic condition, let alone one that requires indefinite drug therapy. Nor did the testimony show that doctors look to the Clinical Studies section to determine the duration of treatment. As Dr. Budoff admitted, "some physicians will find some of the clinical study information helpful, but others will find it irrelevant to their practices." Budoff Tr. 503:2-5. In fact, "some of the data may be completely irrelevant to a prescribing physician." *Id.* at 502:24-503:1 (Budoff).

632. In sum, Plaintiffs have failed to prove that the description of a 12-week trial and its effects in the labelling will induce infringement with respect to the 12-week duration limitation.

4. The patient information and nonclinical toxicology sections of the labelling do not induce infringement of the 12-week limitation.

633. In an abundance of caution, Defendants also address the patient information and nonclinical toxicology sections of the labelling. Plaintiffs relied on these sections as evidence of induced infringement in their summary judgment or pretrial briefs, but failed to establish that either constitutes evidence of induced infringement at trial.

634. Because Plaintiffs presented insufficient evidence at trial regarding these sections, it is not necessary to address them in order to enter judgment for Defendants. Indeed, the Court

previously made clear that neither section "explicitly tell[s] doctors they should prescribe the drug for at least 12 weeks." ECF No. 278 at 9. Nevertheless, for the sake of completeness, the following analysis makes clear that neither section provides any relevant instruction that would lead doctors to administer Defendants' products for at least 12 weeks.

635. First, in their summary judgment and pretrial briefs, Plaintiffs relied on the statement, "Do not change your dose or stop taking icosapent ethyl without talking to your doctor," which appears in the patient information section. No testimony at trial supported the notion that this statement encourages infringement. Dr. Budoff simply stated that the patient information section is "based on . . . what the patient needs to know when starting Vascepa." Budoff Tr. 359:23-24. It is "all lay language on what should the patient do, how should the patient take the medicine, how should the patient store the medicine." *Id.* at 359:19-21 (Budoff). He further explained that the section "describes the medication so that the physician . . . and the patient know[] what it's going to look like." *Id.*at 417:15-20 (Budoff). On cross-examination, however, Dr. Budoff admitted that "[t]his statement is it not instructing doctors and patients so use icosapent for at least 12 weeks," and "doesn't speak to whether the label is encouraging any particular duration." *Id.* at 504:18-505:4 (Budoff); *see also* FF ¶¶ 169-170.

636. On its face, moreover, the statement merely tells patients to "talk" to their doctors, which only begs the question of what their doctors will say. It does not suggest either way whether the doctor should tell a patient to continue the drug or stop it. The Federal Circuit rejected an almost identical argument in *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, 785 F.3d 625 (Fed. Cir. 2015). The patent there required treating gout flares, and the label stated, "If you have a gout flare while taking [the drug], tell your healthcare provider." 785 F.3d at 630. The patentee "argued that this [ ] statement induced infringement because . . . the physician would likely tell the patient to use the [drug] product to treat the acute flare." *Id.* The Federal Circuit, however, rejected this argument, finding that the statement "is neither an explicit nor implicit instruction to take [the drug] for acute gout treatment." *Id.* at 632. Nor would it "'inevitably' lead to physicians who are consulted to advise patients . . . to treat acute gout flares." *Id.* As the Court explained, "vague label language cannot be combined with speculation about how physicians may act to find

inducement. This would seem to too easily transform that which . . . is 'legally irrelevant'—mere knowledge of infringing uses—into induced infringement." *Id*. (quoting *Warner-Lambert*, 316 F.3d at 1364). Although this ruling was in the preliminary-injunction context, the district court on remand relied on this analysis to dismiss the complaint. *See Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, C.A. No. 14-1268-RGA-SRF, 2018 WL 6521922 (D. Del. Dec. 12, 2018).

637. Here, the statement that Plaintiffs previously relied on from the patient information section is even more "vague" than the one in *Takeda*. At least in *Takeda*, the statement actually referred to the infringing condition—"a gout flare." *Id*. Here, the advice "not [to] . . . stop taking icosapent ethyl without talking to your doctor" does not mention any duration of treatment, let alone 12 weeks or longer. The statement is equally consistent with a doctor telling the patient to "stop taking icosapent ethyl" after 11 weeks, or eight weeks, or even two. In short, like the remainder of the labelling, the statement leaves the duration of therapy entirely to the doctor's discretion, and thus does not instruct infringement.

638. Second, in their summary judgment brief (but not in their pretrial brief), Plaintiffs relied on the nonclinical toxicology section of the labelling, which describes carcinogenicity studies in rats and mice that lasted 2 years and 6 months. *See* FF ¶¶ 171-173. At the motion-in-limine stage, Plaintiffs argued, and the Court agreed, that Plaintiffs would be allowed to cross-examine Defendants' experts at trial to elicit evidence that this section of the labelling encourages infringement. ECF No. 315 at 4. Yet Plaintiffs made no such attempt at trial. Thus, as with the patient information section, there is no expert testimony to support the conclusion that the nonclinical toxicology section of the labelling will induce doctors to infringe.

639. Notably, the statements about 2-year and 6-month carcinogenicity studies in the labelling do not even describe an infringing use, much less encourage infringement. The rodents were not given doses of 4 g/day, as required by all asserted claims, but instead received various doses based on their weight. FF ¶ 171. Even if rodents could be considered "subjects" within the meaning of the claims, moreover, there is no indication that they had triglycerides of at least 500 mg/dL. And even if rodent studies were relevant, the same section of the labelling describes other studies that

were shorter than 12 weeks, including rat studies that lasted "9 weeks" and "14 days." FF ¶ 171-172. If anything, these statements suggest that EPA can be administered for shorter time periods than 12 weeks, and cannot lead to the conclusion that the labelling encourages long-term use.

640. Accordingly, Plaintiffs have failed to show that Defendants' labels instruct physicians to administer Defendants' products for at least 12 weeks. As a result, Plaintiffs have not met their burden of proving that Defendants' labels will induce infringement of any asserted claim.

C. All asserted claims are invalid for obviousness.

641. Defendants also have proven by clear and convincing evidence that all 10 asserted claims are invalid as obvious under 35 U.S.C. § 103.

642. Whether a patent claim is obvious is a question of law based on four underlying questions of fact: (a) the level of ordinary skill in the pertinent art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claim; and (d) secondary considerations of nonobviousness. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). The level of ordinary skill and the scope and content of the prior art are addressed in the findings of fact above. FF ¶¶ 255-359. The remaining *Graham* factors are addressed below. Based on all four factors, the asserted claims are invalid as obvious for the following reasons.

643. First, the differences between the asserted claims and the prior art would have been obvious, or at least obvious to try, to a skilled artisan as of the priority date.[14] Second, Plaintiffs' arguments that the prior art did not teach, or taught away from, the claimed invention lack merit. Third, there is no relevant evidence of secondary considerations that weighs against nonobviousness. Each of these reasons is explained in greater depth below.

[14] Plaintiffs did not meet their burden of production to show that the asserted claims were conceived before February 2009, much less by March 25, 2008, as Plaintiffs contend. FF ¶¶ 230-254; *see also* ECF No. 331 ¶ 24 (Plaintiffs' findings of fact). The patents-in-suit are thus entitled to a priority date no earlier than their earliest filing date, i.e., February 10, 2009. The disputed priority date is not material, however, because all asserted claims would have been obvious as of Plaintiffs' alleged conception date in March 2008. Both sides' experts assessed obviousness as of March 2008, and made clear that their opinions would not change if the priority date were February 2009. Heinecke Tr. 827:8-10; Toth Tr. 1638:5-10. Thus, these conclusions of law also address obviousness as of March 2008.

1. The differences between the asserted claims and the prior art would have been obvious to a skilled artisan, or at least obvious to try.

a. A skilled artisan would have been motivated to practice the claimed method of treatment with a reasonable expectation of success.

644. The differences between the prior art's teachings and a claimed invention are obvious if "a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013). "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007).

645. Here, all 10 asserted claims recite the same method of treatment—namely, a method of reducing triglycerides in a patient with triglycerides of at least 500 mg/dL by administering, for at least 12 weeks, about 4 g/day of at least 96% purified EPA. DX 1500 ('728 patent claims 1 and 16); DX 1502 ('715 patent claim 14); DX 1504 ('677 patent claims 1 and 8); DX 1506 ('562 patent claim 1); DX 1514 ('560 patent claims 4 and 17); DX 1516 ('929 patent claims 1 and 5). As articulated by Dr. Heinecke, Defendants' theory for why a skilled artisan would have found this method of treatment obvious is straightforward:

- The Lovaza PDR taught a method of treating patients with triglycerides of at least 500 mg/dL by administering, for at least 12 weeks, 4 g/day of a mixture of EPA and DHA. DX 1535 at 2-3.
- The Lovaza PDR warned, however, that this method of treatment could substantially increase patients' LDL-C levels (at least at a median triglyceride level of 816 mg/dL), which was undesirable. *Id*. at 3.
- Mori taught that DHA increased LDL-C, whereas 4 g/day of 96% purified EPA reduced triglycerides without increasing LDL-C. DX 1538 at 2-3. Other prior art (e.g., Kurabayashi and Hayashi) similarly taught that EPA did not increase LDL-C in patients with triglyceride levels up to 400 mg/dL.
- Thus, the prior art motivated a skilled artisan to substitute the 4 g/day of 96% purified EPA disclosed in Mori for the mixture of EPA and DHA used for the Lovaza indication, with a reasonable expectation that this substitution would avoid the undesirable increase in LDL-C seen with Lovaza use.

Heinecke Tr. 715:10-716:4, 759:10-760:1.

646. The result of this obvious substitution, obtained by combining the Lovaza PDR and Mori, is the method recited in all asserted claims. Although Plaintiffs dispute that the claimed method was obvious, they concede a number of Defendants' key premises. For instance, there is no dispute that the only difference between the method in the Lovaza PDR and the method in the asserted claims is that Lovaza contained a mixture of EPA and DHA, instead of purified EPA. Heinecke Tr. 762:6-14; Toth Tr. 1821:5-1823:1. Nor is there any dispute that the increases in LDL-C caused by Lovaza were known, and that "a skilled artisan would have been motivated to avoid LDL-C increases when treating patients with severe hypertriglyceridemia." Toth Tr. 1822:8-11. Moreover, while "many patients who took Lovaza were also given a statin to address the LDL-C increases," Dr. Toth agreed that since "those patients would have to take two pills, the Lovaza and a statin," "a skilled artisan would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases." *Id*. at 1822:12-21 (Toth); *see also* Heinecke Tr. 813:8-814:2.

647. There is also no serious dispute that a skilled artisan would have wanted to know which active ingredient in Lovaza—EPA or DHA—was responsible for the LDL-C increase (if not both), and that Mori addressed this exact issue. Indeed, Dr. Toth did not dispute that "a skilled artisan seeing that there's DHA and EPA in Lovaza, and seeing a side effect, would at least consider whether the side effect could be associated with only DHA or only EPA." Toth Tr. 1787:6-10. Nor did he dispute that "Mori found that the increase of LDL-C with DHA was statistically significant and the increase with EPA was not." *Id*. at 1788:18-25 (Toth). While Dr. Toth disputed other aspects of Defendants' obviousness defense (addressed further below), the key premises that he conceded lead directly to the motivation and reasonable expectation of success that Defendants have asserted.

648. In addition to the claimed method of treatment, all but one asserted claim (claim 1 of the '929 patent) requires certain effects on a patient's lipids—a minimum reduction in triglycerides

(e.g., at least about 20%);[15] no increase in LDL-C;[16] or a reduction in Apo B.[17] As discussed in the findings of fact above, the prior art showed that purified EPA produced each of the claimed effects in clinical studies. FF ¶¶ 301-307, 324-328, 338-343. In particular, Mori and Hayashi disclosed that EPA reduced triglycerides by at least about 20%; Mori, Hayashi, and Kurabayashi disclosed that EPA did not increase LDL-C; and Kurabayashi disclosed that EPA reduced Apo B. FF ¶¶ 301-307, 324-328, 338-343. (As discussed elsewhere, FF ¶¶ 329-337, there is no dispute that using 4 g/day of 96% purified EPA with a statin, as permitted by seven of the 10 asserted claims, would achieve all of these effects.)

649. One asserted claim (claim 16 of the '728 patent) further requires that the EPA product used to treat the patient contains no more than 0.6% of any other fatty acid. There is no dispute that this level of purity was disclosed and rendered obvious at least by WO '900, which taught a process for producing "99.9% EPA" with "less than 0.1% of DHA." DX 1525 at 17.

650. Critically, in view of the claim language, obviousness is proven as long as there was a reasonable expectation that 4 g/day of 96% purified EPA would achieve the claimed effects (e.g., not cause an LDL-C increase) in patients with triglycerides of *exactly* 500 mg/dL. "It is a long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (quotation omitted). Thus, to prove obviousness, Defendants do not need to prove that a skilled artisan would have reasonably expected success in achieving the claimed effects in patients with triglycerides *above* 500 mg/dL, much less substantially above that level.

651. Also, this case is unlike many other obviousness cases because, when the Patent Office issued the patents-in-suit, it maintained its finding from earlier rejections that the prior art rendered all of the claims prima facie obvious. FF ¶¶ 367-368. As the examiner explained, "it was concluded

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[15] Required by '715 patent claim 14 and '560 patent claims 4 and 17.

[16] As required by '728 patent claims 1 and 16, '715 patent claim 14, '677 patent claims 1 and 8, '652 patent claim 1, and '560 patent claims 4 and 17.

[17] As required by '715 patent claim 14, '677 patent claim 8, and '929 patent claim 5.

that it will be obvious to treat patients having triglycerides above 500 mg/dL with 96% pure ethyl-EPA." DX 1591 at 9. The examiner thus agreed with Defendants' view that the prior art would have motivated a skilled artisan to practice the asserted claims with a reasonable expectation of success (issuing the patents based solely on secondary considerations). Toth Tr. 1804:22-1806:1; FF ¶ 365-369; *see also* ECF No. 331 ¶ 668 (Plaintiffs' proposed findings of fact noting that "the Examiner concluded that it would be prima facie obvious to treat patients having TG above 500 mg/dl with 96% pure ethyl-EPA").

652. The Patent Office correctly interpreted the prior art. Thus, as explained in more depth below for each asserted claim, the prior art that Defendants rely on provided not only a motivation to practice the claimed method, but also a reasonable expectation of achieving every additional limitation of each asserted claim.

b. At a minimum, the claimed method was obvious to try.

i. It was obvious to try substituting purified EPA for the mixture of EPA and DHA in the method of the Lovaza PDR.

653. Even if a skilled artisan had lacked the motivation to use purified EPA, the asserted claims would still be obvious to try. The Supreme Court has held that a claim may be invalid as "obvious to try" where there is "[1] a design need or market pressure to solve a problem and [2] there are a finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421; *see also, e.g.*, *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331-32 (Fed. Cir. 2014) (finding that a claimed drug "dose was obvious to try" where "[t]here was a need to solve the problem of patient compliance by looking to less-frequent dosing regimens" and "there were only a 'finite number of identified, predictable solutions'") (quoting *KSR*, 550 U.S. at 421).

654. Where there is only one difference between the claimed invention and "a particular piece of prior art" that is cited for obviousness, the Federal Circuit has explained that "the obvious-to-try inquiry at least sometimes must focus on known options at what is undisputedly the sole point of novelty in the claim at issue." *Google LLC v. Koninklijke Philips N.V.*, — F. App'x —, 2020 WL 54183, at *4 (Fed. Cir. Jan. 6, 2020) (collecting cases). In this case, it is undisputed that the only difference between the Lovaza PDR and the claimed method of treatment is that Lovaza contained a

mixture of EPA and DHA instead of purified EPA. Thus, the relevant question is whether it was obvious to try purified EPA in the Lovaza PDR's method of treatment. It was.

655. For the first prong of the obvious-to-try inquiry, both sides agree that there was a "need or market pressure to solve a problem"—i.e., to reduce triglycerides in patients with severe hypertriglyceridemia without increasing LDL-C, as reported with Lovaza. *KSR*, 550 U.S. at 421. Again, Dr. Toth admitted that "a skilled artisan would have been motivated to avoid [such] LDL-C increases when treating patients with severe hypertriglyceridemia." Toth Tr. 1822:8-11.

656. For the second prong, there was "a finite number of identified, predictable solutions" to the problem, which included purified EPA. *KSR*, 550 U.S. at 421. As Dr. Toth admitted, "purified EPA, such as Epadel, was given to patients before March 2008 to reduce triglyceride levels," and a skilled artisan "would have found it obvious to use either pure DHA, or pure EPA, to reduce triglyceride levels." Toth Tr. 1823:18-1824:6. In addition, Dr. Heinecke explained that a skilled artisan who was investigating which active ingredient in Lovaza was responsible for the increase in LDL-C would have recognized only three possibilities: "the obvious possibilities were it could be EPA that was a problem, it could be DHA that was a problem, [or] it could be both that were a problem, and so that was very obvious to test." Heinecke Tr. 760:2-761:5. That is "a finite number" of possibilities, which renders the claimed solution—purified EPA—at least obvious to try.

657. Moreover, Dr. Toth testified that an increase in LDL-C was "a common theme" for "the drugs that had already been approved for the management of severe hypertriglyceridemia" by 2008—i.e., Lovaza, fibrates, and niacin. Toth Tr. 1666:18-1667:4. Thus, under Dr. Toth's view of the prior art, a skilled artisan would not have considered those options as solutions to the problem of increased LDL-C. Rather, the options that remained to be tried were purified EPA and purified DHA. This presents a classic case of obvious to try: "At this point, a person having ordinary skill in the art has reached a crossroads where he must choose between two known options. This is a finite number of identified, predictable solutions. . . . The prior art would have funneled the formulator toward these two options; he would not have been required to try all possibilities in a field unreduced by the prior art." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009) (affirming judgment that claimed drug formulation was obvious to try).

658. Indeed, administering purified EPA to patients with severe hypertriglyceridemia had *already* been tried. As Dr. Toth admitted, four prior-art references—Saito, Takaku, Matsuzawa, and Nakamura—each had "at least one patient . . . with triglycerides over 500." Toth Tr. 1862:23-1863:1; FF ¶¶ 340-343. Plaintiffs' statistical expert during prosecution, Dr. Lavin, also admitted that "there must be at least one subject" with triglycerides above 500 mg/dL in Hayashi, contrary to his declaration to the Patent Office. Lavin Dep. Tr. 103:11-21. Thus, it is undisputed that one of the examiner's premises in allowing the claims—that "[t]he prior art does not teach the administration of ethyl-EPA to patients having TG levels between 500 and 1500 mg/dl (very high)"—was mistaken. DX 1591 at 8-9. For the same reason, it was at least obvious to try what others in the prior art had already done—i.e., administer purified EPA to a patient with triglycerides of at least 500 mg/dL. *See Nalpropion Pharm., Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1344, 1354-55 (Fed. Cir. 2019) (rejecting the argument that a skilled artisan would not have found it obvious to try combining two drugs where "[t]he inescapable, real-world fact here is that people of skill in the art *did combine*" them).

ii. It was obvious to try the claimed dose of about 4 g/day.

659. As for the claimed dose of about 4 g/day, both the Lovaza PDR and Mori—Defendants' main combination references—already used that dose, so there is no additional need to show that it was obvious. *See Google*, 2020 WL 54183, at *4 (focusing on whether "the sole contested step of the claim at issue was obvious to try, taking the remaining steps as a given"). Nevertheless, a dose of about 4 g/day was also obvious to try. Indeed, Mori was not the first or only reference to use that dose. As Dr. Toth admitted, "there are at least six prior art references . . . that disclosed the use of 4 grams per day of purified EPA to reduce triglycerides." Toth Tr. 1855:20-25.

660. The claimed dose of about 4 g/day was one of a finite number of options that a skilled artisan would have considered. "Although the universe of potential [EPA] doses is theoretically unlimited," the relevant question in an obvious-to-try analysis is whether there were "a limited number of other doses that had clinical support in the prior art." *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1026 (Fed. Cir. 2018). Here, prior-art studies on purified EPA generally used either the recommended doses for Epadel of 1.8 or 2.7 g/day, or the Mori dose of 4 g/day. FF ¶¶ 344-347. Indeed, the examiner found in the notice of allowance that "96% pure ethyl-EPA has been

administered . . . in order to lower TG in amounts that range from 1.8 g per day up to 4.0 per day." DX 1591 at 9.

661. Similarly, an internal summary of the prior art by Plaintiffs grouped studies on purified EPA into four columns, depending on whether they used 0.9-1.0, 1.8-2, 2.7-3, or 4 g/day. DX 1862 at 93. Plaintiffs concluded that based on the prior art, "doses of 2 to 4 g/day will be at or close to the maximum triglyceride-lowering activity of EPA." *Id*. Plaintiffs included the same grouping and the same conclusion in a filing with the FDA to support their investigational new drug application in June 2008. DX 1816 at 76-77. As Dr. Toth conceded, Plaintiffs' summary was "a reasonable reading of the prior art with regard to dosing," which confirmed that there was "a finite number of available doses for pure EPA." Toth Tr. 1858:4-19.

662. Plaintiffs' summary of prior-art doses also comports with the prior-art WO '118 application, which taught that "[t]he daily dose in terms of EPA-E is typically 0.3 to 6 g/day," as well as a range of "preferabl[e]" doses that included "3.6 g/day." DX 1524 at 35. All of the asserted claims recite a dose of "about" 4 g/day, and there is no dispute that 3.6 g, which is within a 10% difference of 4 g, meets that limitation. Heinecke Tr. 751:3-4.

663. Where, as here, "there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Absent such evidence, the disclosed value in the claim is obvious. *Id*. That is the case here. WO '118 disclosed a range that included about 4 g/day ("0.3 to 6 g/day") and, as discussed further below, there was no teaching away, unexpected results, or other secondary considerations that are pertinent to the claimed dose. Thus, the claimed dose of about 4/g day was obvious, or at least obvious to try.

c. The prior art rendered each asserted claim as a whole obvious.

664. As the Patent Office correctly concluded in the notice of allowance, the differences between the prior art and each asserted claim would have been obvious, or at least obvious to try, to a skilled artisan as of the priority date. DX 1591 at 9. Specifically, as shown below, each asserted

claim was rendered obvious by the combination of the Lovaza PDR, Mori, Hayashi, and Kurabayashi—and, for claim 16 of the '728 patent, WO '900.

i. Claim 1 of the '929 patent

665. Claim 1 of the '929 patent is the broadest asserted claim, because it does not require any specific lipid effect beyond a general reduction in triglycerides. It reads as follows:

> 1. A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl comprising, orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition comprising about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.

666. A skilled artisan would have found the differences between the prior art and claim 1 of the '929 patent obvious, or at least obvious to try, in view of the Lovaza PDR, Mori, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 761:14-764:15.

667. First, the claim is directed to "[a] method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl." This limitation was disclosed by the Lovaza PDR, which taught that "Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels." DX 1535 at 3.

668. Second, the claim requires "orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition." This limitation was also disclosed by the Lovaza PDR, which taught that Lovaza was given by "oral administration," and tested in patients with triglycerides of at least 500 mg/dL in a study lasting "16 weeks." *Id*. at 2-3.

669. Third, the final limitation of the claim requires that the pharmaceutical composition comprises "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids." This is the only difference between the Lovaza PDR and the claim. Although the Lovaza PDR disclosed that "[t]he daily dose of Lovaza is 4 g per day," it also disclosed that "[e]ach one gram capsule of Lovaza" comprises "predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA – approximately 465 mg) and docosahexaenoic acid (DHA

– approximately 375 mg)." *Id*. at 2. In other words, the Lovaza PDR disclosed a 4 g/day dose of a combination of EPA and DHA, instead of a 4 g/day dose of purified EPA.

670. Mori, however, disclosed the third limitation of the claim. In Mori, a group of patients was administered "4 g daily of EPA," which was a "purified preparation[] of EPA ethyl ester (≈96%)." DX 1538 at 2. In other words, Mori disclosed the claimed dose of "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids." Thus, the combination of the Lovaza PDR and Mori disclosed all elements of the claim.

671. Based on the teachings of each reference, a skilled artisan would have been motivated to combine the Lovaza PDR and Mori to arrive at the claimed method. The Lovaza PDR warned that "Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C," so "[p]atients should be monitored to ensure that the LDL-C level does not increase excessively." DX 1535 at 3. In turn, Mori reported the results of a double-blind, placebo-controlled study comparing the effects of EPA and DHA, which showed that "LDL cholesterol increased significantly with DHA . . . , but not with EPA." DX 1538 at 3. In other words, the Lovaza PDR identified a problem (an undesirable increase in LDL-C), and Mori suggested a solution (96% pure EPA). Thus, a skilled artisan would have been motivated to substitute the 4 g/day dose of 96% pure EPA disclosed in Mori for the mixture of EPA and DHA in Lovaza to avoid the increase in LDL-C. Heinecke Tr. 762:21-763:13.

672. In so doing, a skilled artisan would have had a reasonable expectation of success in achieving the claim's only recited effect, "reducing triglycerides." This is because Mori disclosed that triglycerides "reduced significantly by 18.4% with EPA ($P = 0.012$)." DX 1538 at 3.

673. Hayashi and Kurabayashi further supported the motivation to combine and reasonable expectation of success. Hayashi studied the effects of purified EPA in patients with mean triglycerides of "300 ± 233" mg/dL, which included at least one patient with triglycerides above 500 mg/dL. FF ¶¶ 271-273, 338-339. According to Hayashi, "patients treated with ethyl icosapentate showed significant reductions in . . . triglyceride (41%)" levels, with "no statistically significant effect on LDL-C." DX 1532 at 5. Similarly, Kurabayashi tested the effects of 96.5% purified EPA and reported that "[s]erum triglycerides levels decreased significantly" by 27.2% in patients with elevated triglycerides, and that LDL-C levels "were significantly lower at weeks 12, 24, and 48" of

treatment. DX 1534 at 3. Thus, both Hayashi and Kurabayashi corroborated the reasonable expectation provided by Mori that purified EPA would reduce triglycerides without increasing LDL-C. Heinecke Tr. 763:21-11.

674. Accordingly, the differences between the prior art and claim 1 of the '929 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 761:14-764:15.

ii. Claim 5 of the '929 patent

675. Claim 5 of the '929 patent depends from claim 1 of the '929 patent and adds a limitation requiring a reduction in Apo B. Claim 5 reads as follows:

> 5. The method of claim 1, wherein 12 weeks of said daily administration is effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dl.

676. A skilled artisan would have found the differences between the prior art and claim 5 obvious, or at least obvious to try, in view of the Lovaza PDR, Mori, Kurabayashi, and optionally, Hayashi. All of the reasons discussed above for claim 1 of the '929 patent apply equally to claim 5.

677. The only additional limitation in claim 5 requires that the method "is effective to reduce apolipoprotein B." Heinecke Tr. 764:18-21. This limitation was disclosed by Kurabayashi. *Id.* at 764:22-765:2 (Heinecke). As discussed above, Kurabayashi taught that patients treated with over 96.5% purified EPA experienced a 6.9% reduction in Apo B, which was highly statistically significant (with a p-value of less than 0.001). FF ¶¶ 280, 324-326; DX 1534 (Kurabayashi) at 3, 5; Heinecke Tr. 765:3-6.

678. A skilled artisan would have attributed that result to the effects of EPA. Patients taking purified EPA in Kurabayashi were also taking a background therapy of estriol, and the results were compared to patients taking estriol alone, which Kurabayashi called the "control group." DX 1534 at 1. In contrast to the EPA group, which had a highly significant 6.9% reduction in Apo B, there was no significant change in Apo B in the control group. DX 1534 (Kurabayashi) at 4-5; Heinecke Tr. 737:1-23. Moreover, the results reported in Kurabayashi did not suggest any interaction or synergy between EPA and estriol; on the contrary, the two agents had opposite effects on

triglycerides. Heinecke Tr. 735:21-736:9. Thus, a person of ordinary skill in the art would have attributed the significant reduction in Apo B observed in the EPA group to the effects of purified EPA alone. *Id.* at 737:24-738:8 (Heinecke). Indeed, a skilled artisan would have understood that the results in Kurabayashi were consistent with earlier studies on EPA alone, which also showed a statistically significant reduction in Apo B. FF ¶¶ 326-328; DX 1541 (Nozaki 1992) at 4; DX 1530 (Grimsgaard 1997) at 5; Heinecke Tr. 738:18-25.

679. Accordingly, the differences between the prior art and claim 5 of the '929 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, Kurabayashi, and optionally, Hayashi. Heinecke Tr. 765:7-10.

iii. Claim 1 of the '728 patent

680. Claim 1 of the '728 patent is representative of the narrower asserted claims that require particular effects on a patient's lipids. Claim 1 of the '728 patent reads as follows:

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

681. A skilled artisan would have found the differences between the prior art and claim 1 of the '728 patent obvious, or at least obvious to try, in view of the Lovaza PDR, Mori, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 765:13-769:19.

682. First, the claim is directed to "[a] method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl." This limitation was disclosed by the Lovaza PDR, which taught that "Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels." DX 1535 at 3; *see also* Heinecke Tr. 765:22-25.

683. Second, the claim requires "administering orally to the subject about 4g per day of a pharmaceutical composition . . . for a period of 12 weeks." This limitation was also disclosed by the Lovaza PDR, which taught that Lovaza was given by "oral administration," and tested in patients with triglycerides of at least 500 mg/dL in a study lasting "16 weeks." DX 1535 at 2-3; *see also* Heinecke Tr. 766:5-9.

684. Third, the claim requires that the pharmaceutical composition comprise "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters." This is the only difference between the Lovaza PDR and the claim. Although the Lovaza PDR disclosed that "[t]he daily dose of Lovaza is 4 g per day," it also disclosed that "[e]ach one gram capsule of Lovaza" comprises "predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA – approximately 465 mg) and docosahexaenoic acid (DHA – approximately 375 mg)." DX 1535 at 2; *see also* Heinecke Tr. 766:15-19. In other words, the Lovaza PDR disclosed a 4 g/day dose of a combination of EPA and DHA, instead of a 4 g/day dose of purified EPA.

685. Mori, however, disclosed the third limitation of the claim. In Mori, a group of patients was administered "4 g daily of EPA," which was a "purified preparation[] of EPA ethyl ester (≈96%)." DX 1538 at 2; *see also* Heinecke Tr. 766:20-767:2. In other words, Mori disclosed the claimed dose of "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids."

686. Based on the teachings of each reference, a skilled artisan would have been motivated to combine the Lovaza PDR and Mori to arrive at the claimed method. Heinecke Tr. 767:3-10. The Lovaza PDR warned that "Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C," so "[p]atients should be monitored to ensure that the LDL-C level does not increase excessively." DX 1535 at 3; *see also* Heinecke Tr. 767:3-10. In turn, Mori reported the results of a double-blind, placebo-controlled study comparing the effects of EPA and DHA, which showed that "LDL cholesterol increased significantly with DHA . . . , but not with EPA." DX 1538 at 3. In other words, the Lovaza PDR identified a problem (an undesirable increase in LDL-C), and Mori suggested a solution (96% pure EPA). Thus, a skilled artisan would have been motivated to substitute the 4

g/day dose of 96% pure EPA disclosed in Mori for the mixture of EPA and DHA in Lovaza to avoid the increase in LDL-C. Heinecke Tr. 767:3-10.

687. Claim 1 of the '728 patent also requires that the subject being treated is not receiving "concurrent lipid altering therapy" and that the treatment be given "to effect a reduction in triglycerides without substantially increasing LDL-C." Mori also disclosed these limitations. In Mori, "[n]one of the subjects were regularly taking . . . lipid-lowering drugs or other drugs known to affect lipid metabolism." DX 1538 at 2-3. Thus, none of the subjects in Mori were receiving "concurrent lipid altering therapy." Again, Mori showed that triglycerides "decreased significantly by 18.4%" and that "LDL cholesterol increased significantly with DHA . . . , but not with EPA." DX 1538 at 2-3. Thus, Mori disclosed the claimed effects—i.e., "a reduction in triglycerides without substantially increasing LDL-C" in a patient "who does not receive concurrent lipid altering therapy."

688. Finally, claim 1 recites that the effects in the treated subject are "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy." Under the Court's construction of the term "compared to," this phrase "is not a claim limitation," in the sense that it does not "require[] that a practitioner make an actual comparison with another subject or population." ECF No. 135 at 12. Instead, "the claimed effect can be compared to the expectation if the subject did not receive purified ethyl-EPA." ECF No. 135 at 12. Here, based on the prior art, a skilled artisan would have reasonably expected that purified EPA would achieve the claimed effects in a subject, as compared to the expectation if the subject did not receive the drug. Regardless, Mori was a placebo-controlled study that showed the effects of EPA compared to actual "second subject[s]" who were not taking it. DX 1538 at 2-3; Heinecke Tr. 768:16-769:15.

689. Additional references support the reasonable expectation of success for claim 1 of the '728 patent. Hayashi studied the effects of purified EPA in patients with mean triglycerides of "300 ± 233" mg/dL, which included at least one patient with triglycerides above 500 mg/dL. FF ¶ 271. According to Hayashi, "patients treated with ethyl icosapentate showed significant reductions in . . . triglyceride (41%)" levels, with "no statistically significant effect on LDL-C." DX 1532 at 5. Similarly, Kurabayashi tested the effects of 96.5% purified EPA and reported that "[s]erum

triglycerides levels decreased significantly" by 27.2% in patients with elevated triglycerides, and that LDL-C levels "were significantly lower at weeks 12, 24, and 48" of treatment. DX 1534 at 3. Thus, both Hayashi and Kurabayashi corroborated the reasonable expectation provided by Mori that purified EPA would reduce triglycerides without increasing LDL-C. Heinecke Tr. 768:3-15.

690. Accordingly, the differences between the prior art and claim 1 of the '728 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 769:16-19.

iv. Claim 16 of the '728 patent

691. Claim 16 of the '728 patent depends from claim 1 of the '728 patent and adds a limitation requiring a higher EPA purity level. Claim 16 of the '728 patent reads as follows:

> 16. The method of claim 1, wherein no fatty acid of the pharmaceutical composition, except for ethyl- EPA, comprises more than about 0.6% by weight of all fatty acids combined.

692. A skilled artisan would have found the differences between the prior art and claim 1 of the '728 patent obvious, or at least obvious to try, in view of the Lovaza PDR, Mori, WO '900, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 769:20-770:20. All of the reasons discussed above for claim 1 of the '728 patent apply equally to claim 16.

693. The only additional limitation in claim 16 requires that the "pharmaceutical composition, except for ethyl-EPA, comprises more than 0.6% by weight of all fatty acids combined." This further purification level was disclosed and obvious in view of WO '900. WO '900 disclosed a method of purifying EPA that allowed skilled artisans to obtain a "composition compris[ing] between 99.6 and 99.9% EPA, . . . and less than 0.1% of DHA." DX 1525 at 17. Given that a skilled artisan would have been motivated to use purified EPA, for the reasons discussed above, it would have been obvious to use the composition disclosed in WO '900, which was highly purified.

694. Accordingly, the differences between the prior art and claim 16 of the '728 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, WO '900, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 769:20-770:20.

v. Claim 14 of the '715 patent

695. Claim 14 of the '715 patent reads as follows:

> 14. The method of claim 13 comprising administering to the subject about 4 g per day of the pharmaceutical composition to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of LDL-C in the subject.

696. Claim 14 of the '715 patent depends from claim 13. Claim 13 of the '715 patent reads as follows:

> 13. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, comprising administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters for a period of at least 12 weeks to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or apolipoprotein B in the subject.

697. The only difference between claim 13 of the '715 patent and claim 1 of the '728 patent discussed above is that claim 13 requires that the treatment be done "without effecting a statistically significant increase in LDL-C or apolipoprotein B in the subject." Thus, the obviousness analysis above for claim 1 of the '728 patent applies here as well, and is incorporated by reference.

698. The additional limitation, "without effecting a statistically significant increase in LDL-C or apolipoprotein B in the subject," was also known and obvious in view of the prior art. For the same reasons discussed above for claim 1 of the '728 patent, a skilled artisan would have reasonably expected that the claimed method would not effect a statistically significant increase in LDL-C. Further, Kurabayashi taught a statistically significant, 6.9% reduction in Apo B in patients who were treated with over 96.5% purified EPA. FF ¶¶ 280, 324-326; DX 1534 at 3, 5.

699. Again, a skilled artisan would have attributed the significant reduction in Apo B to the effects of EPA. Patients taking purified EPA in Kurabayashi were taking a background therapy of estriol, and the results were compared to patients taking estriol alone, which Kurabayashi called the

"control group." DX 1534 (Kurabayashi) at 1. In contrast to the EPA group, which had a highly significant 6.9% reduction in Apo B, there was no significant change in Apo B in the control group. *Id.* at 4-5; Heinecke Tr. 737:1-23. The results reported in Kurabayashi did not suggest any interaction or synergy between EPA and estriol; on the contrary, the two agents had opposite effects on triglycerides. Heinecke Tr. 735:21-736:9. Thus, a person of ordinary skill in the art would have attributed the significant reduction in Apo B observed in the EPA group to the effects of purified EPA alone. *Id.* at 737:24-738:8 (Heinecke). Indeed, a skilled artisan would have understood that the results in Kurabayashi were consistent with earlier studies on EPA alone, which also showed a statistically significant reduction in Apo B. FF ¶¶ 326-328; DX 1541 (Nozaki 1992) at 4; DX 1530 (Grimsgaard 1997) at 5; Heinecke Tr. 738:18-25.

700. The only limitation that is further added in claim 14 of the '715 patent requires the claimed method "to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of LDL-C in the subject." Again, Kurabayashi taught this limitation. DX 1534. Kurabayashi taught that, in the EPA group, "triglycerides levels decreased," LDL-C levels "were significantly lower[ed]," and Apo B was reduced by 6.9%. DX 1534 at 3, 5; Heinecke Tr. 771:18-25. All of these effects were statistically significant. Thus, "Kurabayashi teach[es] all of the effect limitations in claim 14 of the '715 patent." Heinecke Tr. 772:1-3.

701. Accordingly, the differences between the prior art and claim 14 of the '715 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, and Kurabayashi, and optionally in further combination with Hayashi. Heinecke 770:23-772:7.

vi. Claim 1 of the '677 patent

702. Claim 1 of the '677 patent reads as follows:

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of at least about 12

> weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.

703. The only material difference between claim 1 of the '677 patent and claim 1 of the '728 patent is that claim 1 of the '677 patent does not contain a limitation excluding the use of concurrent lipid-altering therapy. Heinecke Tr. 772:12-18. Claim 1 of the '677 patent is thus broader than claim 1 of the '728 patent, because it includes the same subject matter as claim 1 of the '728 patent, but also covers the treatment of patients who are on concurrent lipid altering therapy. Regardless, it would have been obvious to treat patients with purified EPA regardless of whether they were on concurrent lipid altering therapy. Indeed, both sides' experts testified that this difference did not affect their opinions on obviousness. *Id*. (Heinecke); Toth Tr. 1781:10-20. Because claim 1 of the '677 patent includes the same subject matter, the obviousness analysis discussed above for claim 1 of the '728 patent applies here as well, and is incorporated by reference.

704. Accordingly, the differences between the prior art and claim 1 of the '677 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 772:10-25.

vii. Claim 8 of the '677 patent

705. Claim 8 of the '677 patent depends from claim 1 of the '677 patent and adds a limitation regarding a reduction in Apo B. Claim 8 of the '677 patent reads as follows:

> 8. The method of claim 1, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of at least about 12 weeks to effect a reduction in apolipoprotein B compared to placebo control.

706. The only difference between claim 8 of the '677 patent and claim 1 of the '677 patent discussed above is that claim 8 requires the claimed method "to effect a reduction in apolipoprotein B compared to placebo control." Heinecke Tr. 773:3-10. Thus, the obviousness analysis above for claim 1 of the '677 patent applies here as well, and is incorporated by reference.

707. The additional limitation, "to effect a reduction in apolipoprotein B compared to placebo control," was also known and obvious in view of the prior art. For the same reasons discussed above for claim 5 of the '929 patent and claim 14 of the '715 patent, a skilled artisan would have

reasonably expected that purified EPA would reduce Apo B in view of Kurabayashi, which taught a statistically significant, 6.9% reduction in Apo B in patients who were treated with over 96.5% purified EPA. DX 1534 at 3, 5; *see also* Heinecke Tr. 773:3-13; FF ¶¶ 280, 324-326. This result was compared to a placebo control (i.e., the "control group"), in which there was no significant change in Apo B. DX 1534 at 3, 5. In any event, as discussed above, the Court's construction of the term "compared to" does not require an actual comparison to a placebo group. ECF No. 135 at 12.

708. Accordingly, the differences between the prior art and claim 8 of the '677 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, Kurabayashi, and optionally, Hayashi. Heinecke Tr. 773:1-17.

viii. Claim 1 of the '652 patent

709. Claim 1 of the '652 patent reads as follows:

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline.

710. The only difference between claim 1 of the '652 patent and claim 1 of the '728 patent is that claim 1 of the '652 patent does not contain a limitation restricting the use of concurrent lipid-altering therapy. Heinecke Tr. 773:22-774:4. Claim 1 of the '652 patent is thus broader than claim 1 of the '728 patent, because it includes the same subject matter as claim 1 of the '728 patent, but also covers the treatment of patients who are on concurrent lipid altering therapy. Regardless, it would have been obvious to treat patients with purified EPA regardless of whether they were on concurrent lipid altering therapy. Indeed, both sides' experts testified that this difference did not affect their opinions on obviousness. *Id*. (Heinecke); Toth Tr. 1781:10-20. Because claim 1 of the '652 patent includes the same subject matter, the obviousness analysis discussed above for claim 1 of the '728 patent applies here as well, and is incorporated by reference.

711. Accordingly, the differences between the prior art and claim 1 of the '652 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, and optionally, Hayashi and Kurabayashi. Heinecke Tr. 773:20-774:8.

ix. Claim 4 of the '560 patent

712. Claim 4 of the '560 patent reads as follows:

> 4. The method of claim 1, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject.

713. Claim 4 of the '560 patent depends from claim 1. Claim 1 of the '560 patent reads as follows:

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject.

714. The only difference between claim 1 of the '560 patent and claim 1 of the '728 patent is that claim 1 of the '560 patent does not contain a limitation restricting the use of concurrent lipid-altering therapy and does not contain a limitation regarding LDL-C. Claim 1 of the '560 patent is thus broader than claim 1 of the '728 patent, because it includes the same subject matter as claim 1 of the '728 patent, but also covers the treatment of patients who are on concurrent lipid altering therapy, and covers the treatment of patients even if there is some increase in LDL-C. Because claim 1 of the '560 patent includes the same subject matter, the obviousness analysis discussed above for claim 1 of the '728 patent applies here as well, and is incorporated by reference. Heinecke Tr. 774:16-23.

715. The only limitation that is further added in claim 4 of the '560 patent is that the treatment "effects a reduction in fasting triglycerides of at least 10% without increasing LDL-C by more than 5% in the subject." Mori taught both of these additional limitations. DX1538. Again,

Mori taught that triglycerides "decreased significantly by 18.4% with EPA," and "LDL cholesterol increased significantly with DHA . . . , but not with EPA." *Id.* at 3.

716. For these reasons, the differences between the prior art and claim 4 of the '560 patent would have been obvious to a person of ordinary skill in the art in view of Lovaza PDR, Mori, and Kurabayashi and optionally in further combination with Hayashi. Heinecke Tr. 774:11-775:16.

x. Claim 17 of the '560 patent

717. Claim 17 of the '560 patent reads as follows:

> 17. The method of claim 11, wherein said administering effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control.

718. Claim 17 of the '560 patent depends from claim 11, which reads as follows:

> 11. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject compared to placebo control.

719. There are no material differences between the limitations contained in claim 11 of the '560 patent and claim 1 of the '728 patent. Heinecke Tr. 775:22-776:1. Thus, the obviousness analysis above for claim 1 of the '728 patent applies here as well, and is incorporated by reference.

720. The only limitation that is further added in claim 17 of the '560 patent is that the treatment "effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control." Mori taught this additional limitation. DX1538. Again, Mori taught that triglycerides "decreased significantly by 18.4% with EPA" and "LDL cholesterol increased significantly with DHA . . . , but not with EPA." *Id.* at 3. The claimed reduction in triglycerides of "at least about 20 percent" includes the reduction in triglycerides reported in Mori of 18.4%, which is within a 10% difference of 20%. Heinecke Tr. 776:14-18.

721. Additionally, Hayashi reported a 41% reduction in triglycerides in patients taking purified EPA, which meets the limitation requiring "a reduction in fasting triglycerides of at least

about 20%." DX 1532 at 5. Moreover, patients taking purified EPA in Hayashi experienced no increase in LDL-C. *Id*. In fact, LDL-C was reduced. *Id*.; *see also* Heinecke Tr. 777:2-4.

722. Accordingly, the differences between the prior art and claim 17 of the '560 patent would have been obvious, or at least obvious to try, to a person of ordinary skill in the art in view of the Lovaza PDR, Mori, and Kurabayashi, and optionally in further combination with Hayashi. Heinecke Tr. 775:17-777:8.

2. Plaintiffs' arguments that the prior art was deficient or taught away from the claimed invention lack merit.

723. As discussed above, Dr. Toth conceded the key premises of Defendants' obviousness theory. He agreed that "a skilled artisan would have been motivated to avoid LDL-C increases" with Lovaza. Toth Tr. 1822:8-11. He did not dispute that a skilled artisan "would at least consider whether the side effect could be associated with only DHA or only EPA." *Id.* at 1787:6-10 (Toth). And he did not dispute that Mori addressed this exact issue, concluding "that the increase of LDL-C with DHA was statistically significant and the increase with EPA was not." *Id*. at 1788:18-25 (Toth).

724. Nevertheless, Plaintiffs raise four arguments for why, in their view, a skilled artisan would not have substituted 4 g/day of purified EPA for the mixture of EPA and DHA in Lovaza:

- First, Plaintiffs point to other triglyceride-lowering therapies that increased LDL-C in patients with severe hypertriglyceridemia (e.g., fibrates), and argue that a skilled artisan would not have reasonably expected a different result for purified EPA without seeing clinical data in that specific patient population.
- Second, Plaintiffs argue that even if a skilled artisan had relied on data in patients with triglycerides below 500 mg/dL, the evidence in the prior art was conflicted and did not, as a whole, provide a reasonable expectation of success.
- Third, Plaintiffs argue that a skilled artisan would not have used purified EPA because DHA had other known health benefits, notwithstanding the increase in LDL-C.
- Fourth, Plaintiffs argue that in light of other possible options, neither purified EPA nor a dose of 4 g/day were obvious to try in patients with severe hypertriglyceridemia.

725. In effect, Plaintiffs' view is that despite the teachings of Defendants' asserted references, the prior art as a whole taught away from the claimed method. The Federal Circuit, however, has adopted a strict standard for evaluating whether prior art taught away from a claimed invention: "A reference does not teach away if it does not 'criticize, discredit, or otherwise

discourage' investigation into the invention claimed." *Galderma*, 737 F.3d at 738 (citation omitted; reversing judgment of nonobviousness). As discussed below, Plaintiffs' arguments do not satisfy the strict legal standard for teaching away. Regardless of that standard, Plaintiffs' arguments are both legally and factually flawed, and cannot avoid the conclusion that the prior art would have motivated a skilled artisan to practice the asserted claims with a reasonable expectation of success.

a. Clinical data in patients with triglycerides of at least 500 mg/dL were not needed to form a reasonable expectation of success.

726. Plaintiffs' main argument against finding a reasonable expectation of success is that the prior art lacked data on the LDL-C effects of purified EPA in patients with triglycerides of at least 500 mg/dL. In Plaintiffs' view, a skilled artisan would have expected EPA to work in the same way as other triglyceride-lowering therapies—most notably, fibrates—which increased LDL-C levels in patients with very high triglycerides, even though they did not cause such increases in patients with lower triglyceride levels. According to Plaintiffs, the prior art lacked the necessary data to overcome the expectation that triglyceride-lowering therapy in general would increase LDL-C levels in patients with very high triglycerides. For multiple reasons, Plaintiffs' argument lacks merit.

i. The absence of data in the prior art cannot be a basis to uphold the validity of patents that lack the same data.

727. As a matter of law based on multiple Federal Circuit cases, Plaintiffs cannot dispute a reasonable expectation of success based on a lack of clinical data in the prior art when their own patents do not provide such data. Plaintiffs' argument fails for this reason alone.

728. The Federal Circuit's decision in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), which reversed a judgment of nonobviousness, is instructive. That case involved a method of treating osteoporosis by administering a bisphosphonate compound in a large dose once a week. *Id*. at 1366-67. Before the priority date, bisphosphonates were administered in "small daily doses" because of known difficulties absorbing the drugs, as well as the gastrointestinal side effects of larger doses. *Id*. at 1366. "The inventors trumpeted the reduced-frequency dosing schedule disclosed in the [asserted] patent as decreasing the irritating effect of the compounds, as well as increasing patient compliance with the rigorous dosing instructions." *Id*.

729. The defendant asserted that the claims were obvious over two prior-art articles that suggested testing higher doses of bisphosphonates, at less frequent intervals, to improve patient compliance. *Id*. at 1367-68. The first article stated: "An intermittent treatment program (for example, once per week, or one week every three months), with higher oral dosing, needs to be tested." *Id*. at 1368. The second article stated: "The difficulties with oral bisphosphonates may favor their episodic (once/week) or cyclical (one week each month) administration. [A bisphosphonate] potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs." *Id*. Neither article included any data for its suggested dosing regimen. Both articles simply offered the idea of less frequent regimens with higher doses, without any proof that they would work. Based on that lack of data, the district court upheld the claims as valid. It "distinguished the [prior-art] articles on grounds that they failed to explain how the once-weekly dosing overcame concerns in the art with adverse GI side effects." *Id*. at 1373. In so doing, the district court accepted the patentee's argument that there was an "expectation by physicians in the field" that administering a large bisphosphonate dose "would not be well-tolerated in the prevention and treatment of osteoporosis." *Id*. at 1374.

730. The Federal Circuit reversed. As it explained, this cannot be a sufficient basis to find non-obviousness because "the claimed invention adds nothing beyond the teachings" of the prior art:

> Neither the [asserted] patent nor the [prior-art] articles explain how a higher once-weekly dosing regimen would avoid this set of dose-related adverse side effects. The [asserted] patent sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent. The only data provided in the [ ] patent was generated in beagles, an experiment discredited at trial and disregarded by the district court in its decision. *So while the district court may be correct in finding the [prior-art] articles may have invited skepticism based on concerns for dose-related GI problems, the claimed invention adds nothing beyond the teachings of those articles. Thus, the district court clearly erred in finding any difference between the claimed invention and the articles on this point*.

Id. (emphasis added).

731. Based on this same principle, the Federal Circuit reversed another judgment of nonobviousness in *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362 (Fed. Cir. 2012). The patent there claimed a method of treating eye allergies with the drug olopatadine. *Id*. at 1364. The defendant

asserted that the method was obvious, citing a prior-art study that tested "olopatadine in guinea pig eyes." *Id*. at 1365. The district court, however, upheld the claims as valid, finding that the prior art's "disclosure of using olopatadine eye drops in guinea pigs would not give a skilled artisan an expectation of success because it does not show whether olopatadine is safe to use in the human eye." *Id*.

732. As in *Merck*, however, the Federal Circuit reversed, finding the district court's distinction between the prior art and the asserted patent to be "without merit." *Id*. at 1369. The Federal Circuit explained that "[w]hile it is true that [the prior art] does not expressly disclose that olopatadine would be safe for use in human eyes, neither does the [asserted] patent. The patent is not based on testing in humans; instead it reports only *in vitro* tests of olopatadine in human conjunctival mast cells." *Id*. The Federal Circuit thus "conclude[d] that, *just as a skilled artisan would be able to practice the invention claimed in the [asserted] patent despite its lack of explicit instruction that olopatadine is safe for human ophthalmic use, the artisan would have a reasonable expectation of success for adapting [the prior-art] formulation for the same use in a human eye*." *Id*. (emphasis added).

733. In addition to *Merck* and *Alcon*, the Federal Circuit came to the same conclusion in *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326 (Fed. Cir. 2014). There, similar to the patent in *Merck*, the patent claimed a method of treating osteoporosis with a once-a-month dose of a bisphosphonate. *Id*. at 1327-28. This regimen was purportedly inventive because, according to the patentee, "it was widely believed as of the date of invention that a bisphosphonate regimen with a dose-free interval longer than one or two weeks would not be effective." *Id*. at 1330. In asserting obviousness, the defendant relied on a prior-art study that showed the drug was effective in improving bone mineral density ("BMD") with "a dose-free interval of more than two months." *Id*. at 1331. The patentee criticized this prior art because it disclosed no data on whether the drug reduced bone fractures, which is the main concern with osteoporosis. According to the patentee, "prior art focusing only on BMD and bone-turnover improvements, instead of on antifracture efficacy, does not bear on the obviousness analysis in this case because such prior art does not establish a reasonable expectation of success in reducing fracture risk." *Id*. The Federal Circuit, however, rejected this argument and

held that the claims were obvious. Among other reasons, it found that "[w]hile it is true that BMD improvements do not perfectly correlate with antifracture efficacy," the asserted "patents do not themselves present data demonstrating antifracture efficacy for a once monthly 150 mg dose." *Id*.

734. Beyond these precedents, the District of Delaware's decision in *In re Copaxone Consolidated Cases*, which the Federal Circuit affirmed, applied the same logic to find a thrice-weekly drug dose obvious. No. CV 14-1171-GMS, 2017 WL 401943 (D. Del. Jan. 30, 2017), *aff'd*, 906 F.3d 1013 (Fed. Cir. 2018). There, the patentee argued that a prior-art reference "would not provide those in the art with the motivation to pursue less frequent dosing because 'it provides no data (or even a clinical trial protocol).'" *Id*. at *17. The court, however, rejected this argument, because "the patents-in-suit provided no clinical or pre-clinical data to support a 40mg dose of [the drug] administered three times a week." *Id*. In other words, "the patents-in-suit disclose no additional data beyond the teaching of . . . prior art references." *Id*. Citing *Merck*, the court found that "[i]t would constitute clear error for the court to discredit the [prior art] for the same lack of dosing frequency clinical data from which the patents-in-suit suffer." *Id*. (citing 395 F.3d at 1374).

735. These cases are on point. Plaintiffs criticize Defendants' prior-art references because they do not report data on the LDL-C effects of EPA in patients with triglycerides of at least 500 mg/dL, and thus allegedly fail to overcome an expectation that triglyceride-lowering therapy would increase LDL-C in this patient population. In fact, under Dr. Toth's view, "[a]nything short of a new clinical trial in patients with triglycerides above 500 showing LDL neutrality would be insufficient to provide a reasonable expectation that you will achieve that result." Toth Tr. 1791:20-24. Thus, like the patentees in *Merck*, *Alcon*, *Hoffmann*, and *Copaxone*, Plaintiffs and Dr. Toth criticize the prior art for lacking the clinical data that a skilled artisan would purportedly require to form a reasonable expectation of success. There is no dispute, however, that the patents-in-suit lack the same data that Plaintiffs and Dr. Toth contend are required. In fact, the patents disclose no data of any kind. FF ¶ 16, 252. At least in *Merck* and *Alcon*, the patents included data from animal studies or *in vitro* tests. *See Merck*, 395 F.3d at 1374; *Alcon*, 687 F.3d at 1369. In contrast, the patents here have no data whatsoever—not even animal or *in vitro* data, and certainly no clinical data in patients with severe hypertriglyceridemia. As a result, the prior art that Defendants rely on contains much

more data than the patents. Toth Tr. 1800:14-17. Thus, this is an even stronger case than *Merck* or *Alcon* for rejecting the argument that clinical data are needed for a reasonable expectation of success.

736. At most, the patents include a conclusory prediction that EPA will not increase LDL-C, and a clinical trial protocol for what would later become MARINE. FF ¶¶ 16, 252-253. For example, the specification of each asserted patent states that "[a]pproximately 240 patients *will be* randomized . . . [for a] Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, doubleblind, randomized, placebo-controlled treatment." *E.g.* DX 1500 ('728 patent) at 20. The patent merely provides a laundry list of the possible outcomes of such treatment. *Id*. at 16.

737. But as Dr. Toth conceded, these are not substitutes for data. Under his view, "if a skilled artisan simply reviewed the prior art and came up with a prediction that . . . pure EPA would be LDL-C neutral in patients above 500, that would not be . . . a reasonable prediction of success." Toth Tr. 1792:13-18. Likewise, "even if a skilled artisan came up with a clinical trial protocol that said we're going to use 4 grams pure EPA in patients with triglycerides above 500, and we're hoping that it will be LDL neutral, that would not provide a reasonable expectation of success" under Dr. Toth's view either—not "until the results come out." Toth Tr. 1792:6-12. According to him, "no one was able to reasonably expect the LDL-C neutral effects seen in MARINE until late 2010," when Plaintiffs first received the results. Toth Tr. 1793:5-8. Until then, however, Plaintiffs themselves had no data in patients with triglycerides of at least 500 mg/dL, including when they filed the patent application in February 2009. FF ¶ 252.

738. When pressed on this issue at trial, Dr. Toth's answers were telling:

> Q. Okay. And so to be clear, you're arguing that clinical data is required for a reasonable expectation of success, even though the patent itself contains no clinical data, correct?
>
> A. Well, as I said in my deposition, *I'm sure they had something, but I don't know what it was.*

> Q. Yeah. And that's actually my next question. Under your theory, Amarin had no invention as of 2009 when it filed its patent application, correct?
>
> A. Well, clearly, *they were basing their conclusion on something.*
>
> Q. Now, Doctor, you're here to defend the validity of the patents-in-suit, right?
>
> A. Yes.
>
> Q. And you don't know what the inventors had to support their claims in 2009 that using 4 grams pure EPA in patients above 500 would, in fact, have LDL neutral effects and reduce apo B, correct?
>
> A. *I don't have the data in front of me, no.*

Toth Tr. 1800:19-1801:11 (emphasis added). Whatever that "something" was, it was not clinical data on EPA's LDL-C effects in patients with triglycerides of at least 500 mg/dL. Plaintiffs could not have included such data in the patents, because the data did not even exist when Plaintiffs filed their patent application in February 2009.

739. In short, "the claimed invention adds nothing beyond the teachings of" the prior art with respect to clinical data, and—as the Federal Circuit has held repeatedly—it would be "clearly err[oneous] [to] find[] any difference between the claimed invention and the [prior art] on this point." *Merck*, 395 F.3d at 1374; *see also* FF ¶¶ 16, 252-253. Thus, Plaintiffs cannot point to a lack of prior-art data in patients with triglycerides above 500 mg/dL to uphold the validity of the asserted claims.

ii. A skilled artisan would have reasonably expected similar results in patients with triglycerides of 500 mg/dL.

740. Even apart from the patents' lack of data, Plaintiffs' argument that a skilled artisan would need data in patients with severe hypertriglyceridemia to form a reasonable expectation of success is incorrect. Under Federal Circuit precedent, "[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331. Thus, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (reversing judgment of nonobviousness). In other words, skilled artisans "*can* draw reasonable inferences about the likelihood of success even without

a perfectly designed clinical trial." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) (finding a reasonable expectation of success "[d]espite certain identified shortcomings in the principal references" for defendants' obviousness combination).

741. Here, even if Mori and other studies on patients with lower triglycerides did not provide "conclusive proof" of EPA's effects, they were enough to form "a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331. Indeed, Dr. Toth conceded that skilled artisans could rely on data in patients with triglycerides below 500 mg/dL to make reasonable predictions about how patients above that threshold would respond. As he admitted, "a skilled artisan would know that a drug that reduces triglycerides in a patient at 400, is very likely to also reduce triglycerides in a patient at 600." Toth Tr. 1860:8-11. Thus, there is no dispute that a skilled artisan "would have reasonably expected purified EPA to reduce triglyceride levels above 500," even without data confirming that result. *Id*. at 1860:12-15 (Toth).

742. There was no reason to expect differently for LDL-C. Dr. Toth cited no evidence that the 500 mg/dL threshold reflects any difference in how patients metabolize drugs, or any relationship between that specific threshold and LDL-C. As he admitted, "[t]he 500 threshold was not set because above 500 you are expected to have a greater increase in LDL-C in response to a drug." *Id*. at 1860:3-7 (Toth). Instead, all experts agreed that the threshold simply represents a marker for the risk of pancreatitis, which has nothing to do with LDL-C levels. FF ¶ 285. In Dr. Heinecke's words, there is no "magical mechanistic difference" between having triglycerides of 400, 500, or 600 mg/dL. Heinecke Tr. 796:5-20. A skilled artisan would understand that, regardless of a patient's baseline triglycerides, "the qualitative effects of medications . . . . tend to be the same." *Id*. at 797:16-18 (Heinecke).

743. Apart from lacking any logical or evidentiary basis, the notion that a skilled artisan would disregard clinical data from Mori and other studies simply because they focused on patients with triglycerides below 500 mg/dL is inconsistent with real-world facts—including Plaintiffs' own representations about the prior art outside this litigation.

744. As discussed in the findings of fact above, Plaintiffs repeatedly relied on prior-art studies in patients with triglycerides below 500 mg/dL, including Mori, to show that purified EPA is

LDL-C neutral in patients with higher triglyceride levels. FF ¶¶ 317, 319. As shown below, in an investor presentation dated March 2010—before Plaintiffs had results from MARINE—Plaintiffs represented that "Multiple Studies Demonstrate that DHA Raises LDL-C," and "Multiple Studies Demonstrate that EPA is LDL Neutral." DX 1800 at 12-13.

Multiple Studies Demonstrate that DHA Raises LDL-C

Study author and year	DHA treatment	Treatment duration	Baseline TG	Change in TG	Baseline LDL mg/dl	Change in LDL
Kelley 2007	3g	90 days	248	-24.4%	120	+13.5%
Maki 2005	1.5g	6 weeks	179	-21.4%	142	+12.0%
Theobald 2004	1.5g	3 months	92	-2%	122	+10.1%
Geppert 2006	2.28g	8 weeks	96	-23.2%	95	+10.6%
Sanders 2006	1.5g	4 weeks	96	-13.9%	97	+6.7%
Engler 2004	1.2g	6 months	139	-9.9%	201	+14%
Nestel 2002	2.8g	7 weeks	176	-32%	176	+3.8%

Multiple Studies Demonstrate that EPA is LDL Neutral

Study author and year	EPA treatment	Treatment duration	Baseline TG	Change in TG	Baseline LDL mg/dl	Change in LDL
Kurabayashi 2000	1800	48 weeks	136	-13.8%	165	-5.88%
Yamashita 1995	1800	8 weeks	161	-24.8%	139.5	-4.66%
Ando 1999	1800	3 months	260	-42.1%	144	-15.72%
Mori 2000	4000	6 weeks	179	-18.4%	172	0.00%
Grimsgaard 1997	4000	7 weeks	109	-12.2%	158	-1.97%
Woodman 2002	4000	6 weeks	119	-17.1%	104	0.75%

DX 1800 at 12, 13.

745. All of the studies that Plaintiffs cited, which included Mori and Kurabayashi, were prior art. *Id.* Plaintiffs did not qualify their representations about the prior art by stating that the results applied only to patients with triglycerides below 500 mg/dL. On the contrary, Plaintiffs made clear to investors that these prior-art findings applied to the intended indications for Vascepa,

including for patients with triglycerides of ">500 mg/dl." *Id*. at 10; *see also id*. at 16 ("Population: Patients with very high triglycerides (≥500 mg/dL"). Plaintiffs' fact and expert witnesses agreed that these representations to investors were accurate and did not mischaracterize the prior art. FF ¶¶ 382-387.

746. Even after Vascepa was approved to treat patients with triglycerides of at least 500 mg/dL, Plaintiffs continued to rely on Mori as relevant evidence for that patient population. In a citizen petition to Plaintiffs' regulator (the FDA) regarding Vascepa, Plaintiffs represented that "[t]he data from [Mori] support . . . that EPA and DHA have differential effects on other well-studied lipid parameters such as LDL-C and HDL-C." DX 2104 at 9. Again, Plaintiffs did not qualify that representation to their regulator by stating that Mori's results were irrelevant to patients with higher triglyceride levels. If that were Plaintiffs' view, they would not have cited Mori in a citizen petition filed with the FDA about Vascepa, which was indicated only to treat patients with severe hypertriglyceridemia. *Id*. at 3.

747. While these statements by Plaintiffs are not themselves prior art, they provide evidence of how a skilled artisan would view and interpret the prior art—including whether Plaintiffs are now correct in arguing that a skilled artisan would discount prior-art data on patients with triglycerides below 500 mg/dL. Indeed, the Federal Circuit has approved using evidence that is not technically prior art, including a patentee's previous representations to the FDA and internal documents, to rebut a patentee's contrary arguments about what was known in the art. *See, e.g.*, *Pfizer*, 480 F.3d at 1359 (rejecting Pfizer's argument that the effects of a claimed pharmaceutical salt were unpredictable without data, where "there is a suggestion in Pfizer's supplemental filing with the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose"); *Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572, 1580-81 (Fed. Cir. 1983) (relying on patentee's "unpublished internal criteria" as evidence of "the knowledge of one of ordinary skill in the art"). Regardless, Dr. Toth conceded that Plaintiffs' internal documents and non-public statements to its investors did not mischaracterize the prior art. Toth Tr. 1834:13-16, 1836:14-17.

748. As for the prior art itself, both sides have cited many references on purified EPA, including on its LDL-C effects, and not a single reference suggested that those effects would differ

in patients with triglycerides of at least 500 mg/dL. If anything, the prior art suggested the effects would be consistent. For example, Hayashi broadly concluded that "purified [EPA] apparently has no deleterious effect of plasma LDL-C" in the studied patient population, which Dr. Lavin agreed included at least one patient with triglycerides above 500 mg/dL. DX 1532 at 7. At a minimum, Dr. Toth agreed that Hayashi included patients with triglycerides of 425 and 375 mg/dL. Toth Tr. 1655:21-1656:2; DX 1532 at 7, fig. 2. Although he disputed that Hayashi could reliably measure LDL-C in patients with triglycerides above 400 mg/dL, the fact remains that Hayashi reported no LDL-C increase overall, including for patients with triglycerides very close to that threshold. There was no reason for a skilled artisan to believe that this result would suddenly change when triglycerides increased from 400 to 500 mg/dL. Indeed, Hayashi did not qualify its conclusion by adding that different results were expected at higher triglyceride levels—even though at least one patient, and likely more than one, had triglycerides above 500 mg/dL. FF ¶¶ 269-275. Nor did Mori or Kurabayashi.

749. In addition, whereas the label for Lovaza warned about LDL-C increases in patients with triglycerides of at least 500 mg/dL, the label for Epadel (which contained purified EPA) did not. FF ¶ 305. At the time, Epadel was indicated to treat "an excess of triglycerides"—with no upper limit—and the labelling cited at least two prior-art studies in which patients with triglycerides above 500 mg/dL were administered purified EPA (Takaku and Matsuzawa). DX 1528 at 2, 8; FF ¶¶ 341-343. Yet there was no warning in the Epadel label to expect different effects, or LDL-C increases, in patients with very high triglycerides. As Dr. Toth admitted, "there's nothing in the Epadel label that warns about LDL-C increases." Toth Tr. 1824:7-9. Indeed, Plaintiffs' internal documents predating the alleged priority date noted this exact difference: While "the FDA required [warnings about LDL-C] to be included in Lovaza's package insert," "there is no reference to Epadel treatment causing LDL elevation in Epadel's package insert." DX 1829 at 4-5.

750. Even the FDA, which limited Lovaza's approval to patients with triglycerides of at least 500 mg/dL, did not discount studies on patients with lower triglycerides. In fact, the Clinical Studies section of the Lovaza PDR included a study on the combined effects of Lovaza and a statin in patients with "High Triglycerides (200 to 499 mg/dL)." DX 1535 at 2. Plaintiffs cannot assert

that this study is only relevant to patients with triglycerides below 500 mg/dL. The FDA's guidance on Clinical Studies sections, which Plaintiffs rely on for their infringement case, lists "[c]linical studies with results that imply effectiveness for an unapproved indication" as examples of "Studies *Not* To Include in the Clinical Studies Section." PX 776 at 6. Thus, if the FDA had viewed studies on patients with triglycerides below 500 mg/dL as irrelevant to patients with higher triglycerides, that study would not have been included in the Clinical Studies section of the Lovaza PDR.

iii. Data on Lovaza, fibrates, and niacin did not teach away or alter the reasonable expectation that EPA would produce similar effects in patients with triglycerides of 500 mg/dL.

751. The prior-art references that Plaintiffs rely on as purportedly showing a different expectation in patients with triglycerides of 500 mg/dL do not change the result. Plaintiffs cite no prior art suggesting that purified EPA has different effects on LDL-C in such patients. At most, they rely on references about the effects of *other* drugs, on patients with triglyceride levels *far above* 500. Specifically, Plaintiffs cite data from the label for Tricor (a fibrate) and the statistical review for Lovaza, which showed that these drugs increased LDL-C in patients with mean triglycerides of 726 and 816 mg/dL, respectively. PDX 6-7 (citing PX 388 at 6-7), PDX 6-8 (citing PX 939). Plaintiffs also cite the Carlson reference from 1977, which reported that niacin increased LDL-C in just five patients with severe hypertriglyceridemia, whose baseline triglycerides were not reported. PX 1026 at 3. Based on these references, Dr. Toth opined that increases in LDL-C were a "common theme" among triglyceride-lowering drugs. Toth Tr. 1666:18-1667:4.

752. None of Plaintiffs' references, however, "criticize, discredit, or otherwise discourage" using purified EPA in the method of the Lovaza PDR—the motivation that Defendants assert would have rendered the asserted claims obvious to a skilled artisan. *Galderma*, 737 F.3d at 739. Indeed, none of these references even mention purified EPA. Toth Tr. 1804:13-20. Thus, as a matter of law, they "do[] not teach away." *Galderma*, 737 F.3d at 739. Even if a skilled artisan had considered them, they would not have altered the reasonable expectation that purified EPA would reduce triglycerides without increasing LDL-C—for several independent reasons.

753. First, a skilled artisan would not have relied on data regarding Lovaza, a mixture of EPA and DHA, to predict the effects of EPA alone. As Dr. Toth admitted, the prior art showed that

EPA and DHA "clearly had some different effects." Toth Tr. 1829:6-8. Thus, "the fact that Lovaza itself has an LDL-C side effect doesn't answer the question of whether that side effect could be attributed to solely EPA or solely DHA." *Id*. at 1801:21-25 (Toth). The data that Plaintiffs cite, moreover, showed that Lovaza increased LDL-C in patients with triglycerides both above and below the 500 mg/dL threshold. PDX 6-8. That result is consistent with Mori and Defendants' obviousness theory. Given that Lovaza was a mixture of EPA and DHA, the fact that it increased LDL-C merely begged the question of which ingredient was responsible for that effect. As discussed, Mori (particularly when read with Hayashi and Kurabayashi) suggested that DHA, not EPA, caused the increase in LDL-C. The rise in LDL-C with Lovaza is thus consistent with the reasonable expectation that EPA alone would not increase LDL-C.

754. Second, the fact that fibrates and Lovaza increased LDL-C in patients with triglycerides far above 500 mg/dL (726 and 816 mg/dL) does not address the relevant question, which is whether LDL-C increases were expected at *any* triglyceride level of 500 mg/dL or more. "It is a long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo*, 793 F.3d at 1281 (quotation omitted). None of the asserted claims are limited to treating patients with triglycerides above 700 mg/dL. They all include treating patients with triglycerides as low as 500 mg/dL. Thus, even if it were unexpected for EPA to avoid increasing LDL-C in patients with triglycerides above 700 mg/dL, the claims would still be invalid because EPA was reasonably expected to avoid increasing LDL-C in patients whose triglycerides were exactly 500 mg/dL.

755. Plaintiffs' data on fibrates are consistent with that expectation. While LDL-C increased in patients with mean triglycerides of 726 mg/dL, there was no statistically significant increase in patients with mean triglycerides of 432 mg/dL, which is much closer to the 500 mg/dL threshold than 726 mg/dL. PX 388 at 7; PDX 6-7. Thus, even if a skilled artisan would have relied on data regarding fibrates, she would have reasonably expected that LDL-C would not increase in a patient with triglycerides of 500 mg/dL, which is enough to render all asserted claims obvious.

756. Third, in any event, a skilled artisan would not have expected purified EPA to have the same effects as fibrates or niacin. Indeed, Dr. Toth "did not cite . . . any prior art comparing the

LDL-C effects of niacin or fibrates on the one hand with pure EPA." Toth Tr. 1804:17-20. Nor did he cite any evidence to suggest that EPA and fibrates or niacin have any structural relationship or share the same mechanisms of action. In fact, Plaintiffs' initial new drug application package to the FDA, dated June 2008, suggested the opposite: "The mechanisms with which TG lowering therapies such as fibrates or niacin exert their effects are fairly well established; however, a mechanism to explain the hypotriglyceridemic effects of omega-3 fatty acids has not been clarified." DX 1816 at 9-10.

757. During prosecution, the Patent Office expressly rejected Plaintiffs' analogy between fibrates and EPA, in a finding that was never retracted. As the examiner explained: "Triplix (fenofibric acid) is structurally and biologically very different from EPA-E (an omega-3 fatty acid)," so "one cannot extrapolate the results observed with a fibrate (Triplix) to omega-3 fatty acids like EPA-E." DX 1587 at 19. Although Dr. Toth disagreed with the examiner's conclusion, he never disputed that fibrates are, in fact, "structurally and biologically very different" from EPA. *Id.* Likewise, neither Dr. Toth nor any other witness rebutted Dr. Heinecke's testimony that niacin and EPA have no structural relationship "whatsoever." Heinecke Tr. 911:23-912:4.

758. At most, Plaintiffs cited general statements that fibrates, niacin, and *mixtures* of EPA and DHA enhance the conversion of VLDL to LDL, among other effects. *E.g.*, PX 923 (McKenney 2007) at 5. Again, however, the fact that fibrates or niacin were compared to mixtures of EPA and DHA, such as Lovaza, does not address the expected effects of EPA alone. The notion that Lovaza may work similarly to fibrates or niacin is consistent with Mori, which suggested that one component of Lovaza—DHA—was responsible for the increase in LDL-C.

759. Fourth, even if it were proper to compare purified EPA to other drugs, the notion that all triglyceride-lowering drugs increase LDL-C in patients with severe hypertriglyceridemia is incorrect. Based on the evidence, a skilled artisan would not have had that expectation.

760. Plaintiffs' only evidence that niacin increases LDL-C, the 1977 Carlson paper, involved only five patients taking niacin, and did not report those patients' baseline triglycerides. PX 1026 at 3. Notably, the ATP-III guidelines, which both sides treated as authoritative, did not suggest that niacin would raise LDL-C in such patients. This is despite the fact that ATP-III's entry for

fibrates expressly noted that LDL-C decreases "in nonhypertriglyceridemic persons," but "may be increased in hypertriglyceridemic persons." DX 1876 at 175. By contrast, the entry for niacin stated simply that "[n]icotinic acid lowers serum total and LDL-cholesterol," with no mention of a different result in patients with elevated triglycerides. *Id*. at 172. Based on ATP-III, differential effects on LDL-C between patients with lower and higher triglycerides were not a "common theme" among triglyceride-lowering drugs. Toth Tr. 1666:18-1667:4. If anything, fibrates were the outlier.

761. Plaintiffs and Dr. Toth also failed to account for statins, which further contradict the notion that all triglyceride-lowering therapies were known to raise LDL-C. For example, the approved label for Lipitor (atorvastatin) in 2007 reported a clinical trial in which the "median (min, max) baseline TG level was 565 (267-1502)"—i.e., a median of 565 mg/dL, with a range of up to 1502 mg/dL. DX 1986 (current Lipitor label) at 21; *see also* DX 3007 (2007 Lipitor label) at 11-12. In that trial, all doses of Lipitor reduced triglycerides *and* LDL-C. *Id*. Even the lowest dose of 10 mg, for example, reduced median triglycerides by 41% and LDL-C by 26.5%. *Id*. Thus, a skilled artisan would have understood that a triglyceride-lowering therapy could, in fact, effectively lower triglycerides without also increasing LDL-C. Indeed, such a therapy could even *reduce* LDL-C.

762. Plaintiffs and Dr. Toth tried to minimize the Lipitor label by contending that Lipitor was not specifically approved to treat severe hypertriglyceridemia, and that statins in general were not favored as effective triglyceride-lowering drugs. Even if these contentions were true, however, they would not change the fact that Lipitor disproves Dr. Toth's theory that all triglyceride-lowering drugs increased LDL-C in patients with severe hypertriglyceridemia.

763. Plaintiffs' contentions, moreover, were not true. Lipitor was in fact indicated "as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV)." DX 1986 (current Lipitor label) at 2; DX 3007 (2007 Lipitor label) at 14. While Dr. Toth testified that Type IV patients were "typically under 500," he admitted that at least some patients had triglycerides of 500 mg/dL or higher. Toth Tr. 1581:7-10, 1813:10-21. And regardless of Dr. Toth's testimony, the patients in the clinical study on the label that was titled "Hypertriglyceridemia (*Fredrickson* Type IV)" had median triglycerides above 500 mg/dL, so it is clear that the FDA considered Type IV to include patients with those triglyceride levels. DX 3007 (2007 Lipitor Label)

at 11; DX 1986 (Current Lipitor Label) at 21. Indeed, the statistical review for Lovaza that Dr. Toth relied on for data in patients with triglycerides of at least 500 mg/dL also labeled the patients in those studies as having "Type IV" hyperlipidemia. PX 939 (Lovaza statistical review) at 5.

764. The Lipitor label also belies Plaintiffs' contention that statins were not effective at reducing triglycerides. Again, even the lowest dose (10 mg) reduced triglycerides by a median of 41%, which is even higher than the reduction achieved by Vascepa. *Compare* DX 3007 (2007 Lipitor label) at 12 *with* DX 1741 (Bays 2011) at 1. At most, the evidence shows that fibrates or other more potent triglyceride-lowering drugs were preferred in patients with much higher triglyceride levels—above 1,000 mg/dL—but that statins were a suitable choice for most patients above 500 mg/dL. As stated in Karalis, treatment guidelines "recommend[ed] that when TG levels are ≥1000 mg/dL an agent that primarily lowers TG such as prescription omega-3 fatty acids and fibrates be used as first-line therapy; *however, in patients with TG levels of 500–999 mg/dL*, if there is no history of pancreatitis *a statin may also be considered as first-line therapy*." DX 1957 at 9 (emphasis added). Thus, Plaintiffs' argument that statins were not a suitable triglyceride-lowering drug is incorrect and, in any event, irrelevant.

b. Plaintiffs cannot avoid the reasonable expectation that DHA, not EPA, was responsible for the rise in LDL-C seen with Lovaza.

765. Once it becomes clear that LDL-C data in patients with triglycerides of at least 500 mg/dL are not required for a reasonable expectation of success, it becomes equally clear that the prior art provided that expectation. Mori, Hayashi, Kurabayashi, as well as many background references were consistent in showing that EPA did not increase (or even reduced) LDL-C. FF ¶¶ 304-305. Plaintiffs' attempts to undermine or contradict these studies lack merit.

i. Plaintiffs' criticisms of Mori and other prior art lack merit.

766. Despite the fact that Mori was a double-blind, placebo-controlled study in humans, both Dr. Toth and Dr. Ketchum criticized its reliability. Dr. Toth called Mori a "small" study, and Dr. Ketchum emphasized that it was "not FDA reviewed" and lacked "regulatory gravitas." Toth Tr. 1643:20-22; Ketchum Tr. 201:4-25. These criticisms do not defeat the reasonable expectation of success. Again, as the Federal Circuit has made clear, skilled artisans "*can* draw reasonable

inferences about the likelihood of success even without a perfectly designed clinical trial." *Acorda*, 903 F.3d at 1334. Nor is there any requirement that prior-art studies meet the exacting standards required by the FDA. "There is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval. Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). The fact that a prior-art study has some flaws cannot avoid obviousness, because "only a reasonable expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d at 1364.

767. Moreover, criticizing Mori in isolation ignores that its conclusion that EPA does not increase LDL-C was corroborated by Hayashi and Kurabayashi, as well as numerous background references, which "legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015); FF ¶¶ 301-305; *see also Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (vacating nonobviousness finding that "narrowly focus[ed] on the four prior-art references cited" in obviousness combinations and "failed to account for critical background information that could easily explain why an ordinarily skilled artisan would have been motivated to combine or modify the cited references to arrive at the claimed inventions").

768. Plaintiffs cannot seriously dispute the reliability or conclusions of Defendants' prior-art references given Plaintiffs' own representations to investors and the FDA. As discussed above, Plaintiffs made clear that, even though Mori and Kurabayashi did not test patients with triglycerides of at least 500 mg/dL, their findings were relevant to that patient population. Plaintiffs were equally clear in representing those studies' reported effects on LDL-C. FF ¶¶ 382-386. Again, Plaintiffs told investors that both Mori and Kurabayashi, among other studies, "*Demonstrate* that EPA is LDL Neutral." DX 1800 at 13 (emphasis added). And just months after the alleged priority date in 2008, Plaintiffs told the FDA that "[i]n clinical studies performed with Ethyl-EPA to date . . . there is no evidence of a significant rise in LDL-cholesterol." DX 1816 at 85. These representations were unambiguous, and comport with how a skilled artisan would understand the prior art.

769. The publication for Plaintiffs' MARINE study also cited Mori as showing that "although DHA treatment generally increased LDL cholesterol levels, EPA therapy did not," and cited Kurabayashi as "suggest[ing] that purified EPA might reduce TG levels without increasing LDL cholesterol levels." DX 1741 at 1, 7, 9; *see also* DX 1829 at 11 (internal appendix stating that Mori showed no significant LDL-C effect with EPA). As with Plaintiffs' internal analyses and FDA filings, Plaintiffs' post-priority publication is also relevant to rebutting their criticisms of the prior art and understanding how skilled artisans would interpret the prior art. *See Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) ("We have approved use of later publications as evidence of the state of art existing on the filing date.") (quotation omitted).

ii. Plaintiffs' cited studies did not teach away from a reasonable expectation of success based on the prior art as a whole.

770. Despite their previous representations, Plaintiffs now cite other prior-art references—which were never cited in their research publications, internal documents, investor presentations, or FDA filings—that purportedly contradict Mori's conclusion. Specifically, Plaintiffs cite Rambjør 1996 (DX 1961) and von Schacky 2006 (DX 1605) as purportedly teaching that EPA increases LDL-C, as well as Agren 1996 (DX 1933) and Conquer 1996 (DX 1949) as purportedly teaching that DHA was LDL-neutral. As discussed below, however, these references do not support Plaintiffs' position or alter the motivation to use purified EPA with a reasonable expectation of success.

771. First, as with Plaintiffs' references on other triglyceride-lowering therapies discussed above, none of Plaintiffs' references on the LDL-C effects of EPA or DHA teach away from the claimed invention. That is, these references do not "criticize, discredit, or otherwise discourage" using purified EPA to treat patients with severe hypertriglyceridemia. *Galderma*, 737 F.3d at 739.

772. The only reference that actually tested EPA and DHA is Rambjør, and it concluded that only EPA was effective for reducing triglycerides. As Rambjør concluded, "EPA produced significant decreases" in triglycerides, whereas "DHA supplementation did not affect" them. DX 1961 at 3. Nothing in the reference criticizes, discredits, or otherwise discourages using purified EPA. If anything, Rambjør suggested that as between EPA and DHA, only EPA would be an effective therapy, which would teach away from DHA, not EPA. FF ¶ 308.

773. As for von Schacky, it merely compared various effects of EPA and DHA that were purportedly reported in previous studies, without providing any new data on either compound, and did not criticize, discredit, or otherwise discourage the use of either EPA or DHA. FF ¶ 311.

774. Similarly, Agren and Conquer did not test EPA. Both studied DHA alone, and thus did not provide any data for, let alone teach away from, purified EPA. FF ¶ 307.

775. Second, even if any of these references taught away (they did not), that would not defeat obviousness here. As the Federal Circuit has made clear, "there is no rule that a single reference that teaches away will mandate a finding of nonobviousness. . . . Where the prior art contains apparently conflicting teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill considering the degree to which one reference might accurately discredit another." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Thus, the Federal Circuit has rejected teaching away arguments based on "isolated prior art disclosures" where "the prior art as a whole . . . d[id] not teach away." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 834 (Fed. Cir. 2015).

776. Here, the weight of the evidence shows that a skilled artisan would not have relied on these "isolated prior art disclosures," much less viewed them as rebutting Mori's express conclusion that purified EPA reduced triglycerides without increasing LDL-C.

777. As to Rambjør, the article itself warned readers against drawing any conclusions from the study about the comparative effects of EPA and DHA. The authors explained that "the DHA group was relatively small (n = 9[])" and "thus underpowered" to detect statistically significant changes. DX 1961 at 4. Indeed, "the percent change in LDL C was identical for both EPA and DHA (+6%), but the smaller number of subjects in the latter group prevented the difference from being significant." *Id*. In other words, the study was not equipped to compare the differences between EPA and DHA. Rather than draw any definitive conclusions from the data, the authors made clear that "[f]urther studies are needed to clearly define individual effects of EPA and DHA." *Id*. at 6.

778. Rambjør was published in 1996, and thus one of the "[f]urther studies" that followed it "to clearly define individual effects of EPA and DHA" was Mori, which was published in 2000.

Id. Mori in fact addressed Rambjør, and expressly criticized the study's design. As Mori explained, Rambjør "had only a small number of subjects in the DHA group, was short in duration, and included only a 2-wk washout period between treatments." DX 1538 at 5, 9 (endnote 16 citing Rambjør). Especially since both Rambjør itself and Mori expressly criticized Rambjør's study design, a skilled artisan as of 2008 would not have continued to relied on Rambjør's 1996 data after Mori's more recent results from 2000 were published. Heinecke Tr. 782:4-785:2.

779. Even apart from Rambjør's design flaws, a skilled artisan would have found Mori to be much more instructive than Rambjør for purposes of evaluating the expected effects of 4 g/day of 96% pure EPA. Again, Mori tested that exact dose and purity. DX 1538 at 2. By contrast, Rambjør tested a lower dose (3 g/day) and a lower purity (91%). DX 1961 at 1; Toth Tr. 1841:11-25. Thus, to the extent a skilled artisan perceived a conflict between the results of Mori and Rambjør, she would have relied on the more relevant results in Mori rather than those in Rambjør.

780. As to von Schacky, experts on both sides agreed that it was only a review article summarizing previous studies, and did not provide any new data comparing EPA and DHA. Heinecke Tr. 785:7-12; Toth Tr. 1844:9-17. As Dr. Toth agreed, von Schacky simply offered the author's "interpretation" of previous data, whereas a skilled artisan "would look at the underlying clinical studies" themselves. Toth Tr. 1847:25-1848:8. von Schacky is thus irrelevant to the expectations of a skilled artisan, who would rely on actual data and clinical studies, not one author's "interpretation."

781. Even if a skilled artisan had looked to von Schacky, she would not have relied on its conclusions. According to Plaintiffs, Table 1 in von Schacky taught that EPA increased LDL-C because it included a "↑" symbol in the row for LDL-C and the column for EPA. DX 1605 at 9, Tbl. 1. The table's heading, however, states only that the "[a]rrows reflect *semi-quantitatively* the findings from the literature." *Id*. (emphasis added). Moreover, the cited "literature" for the table included both Rambjør, which was discredited by the time von Schacky was published, as well as Mori, which contradicted von Schacky's "↑" symbol by concluding that EPA had no statistically significant effect on LDL-C. In fact, the body of the article revealed that von Schacky entirely misconstrued Mori. von Schacky cited Mori for the proposition that "[i]n more recent comparative studies, no effects of

either EPA or DHA were seen on LDL levels." DX 1605 at 5. But as Dr. Toth admitted, "[t]hat's not what Mori says." Toth Tr. 1847:8-17. Nor is it even internally consistent with the Table 1, which includes a "↑" symbol for both EPA and DHA. DX 1605 at 9. Thus, a skilled artisan would not have viewed von Schacky as a reliable source, and it would not have changed a skilled artisan's opinions about the actual clinical data and conclusions reported in Mori. Heinecke Tr. 785:23-787:5. Rather, "a skilled artisan as of March 2008, looking at the literature, including the von Schacky reference, would look at the underlying clinical studies, such as Mori." Toth Tr. 1848:4-8.

782. As to Agren and Conquer, again, neither reference studied EPA. Agren compared only "fish diet, fish oil and DHA-oil" (DX 1933 at 4), and Conquer only tested "an algae source of docosahexaenoic acid . . . devoid of any eicosapentaenoic acid." DX 1949 at 1. Thus, a skilled artisan would not have relied on either Agren or Conquer to compare the results of EPA and DHA on LDL-C. Heinecke Tr. 778:21-780:23. Even as to DHA alone, Agren made clear that "the only definite conclusion which can be made on the basis of this study is that [ ] DHA is effective in lowering fasting plasma triglyceride concentrations." DX 1933 at 6. The study drew no "definite conclusion" about DHA's effects on LDL-C.

783. Moreover, like Rambjør, both Agren and Conquer were published in 1996, before Mori and a number of other references on EPA and DHA were published. In 2005, Maki surveyed previous studies and concluded that "[m]ost studies of DHA supplementation have shown increases in LDL cholesterol concentrations with net LDL cholesterol responses ranging from -2.8% to 16.0% (median = 7.2%)." DX 1536 at 9. Thus, despite some outliers like Agren and Conquer, the prior art as a whole taught that DHA in fact did increase LDL-C.

784. In the end, the only reference that Plaintiffs have cited with any clinical data suggesting that purified EPA increases LDL-C is Rambjør—a study that predated Mori's results, used a lower and less pure dose, and was criticized by both Mori and the authors of Rambjør itself. By contrast, Mori, Hayashi, and Kurabayashi—as well as at least four background references discussed above—consistently reported that purified EPA did not increase LDL-C, and sometimes even reduced it. FF ¶¶ 301-308. Considering the prior art as a whole, the weight of the evidence thus supported the reasonable expectation that purified EPA would not increase LDL-C. As Dr. Heinecke explained,

moreover, the fact that some studies reported an increase in LDL-C and some showed a reduction in LDL-C is actually consistent with, and in fact "very strong evidence" to support, the conclusion that purified EPA was LDL-C neutral. Heinecke Tr. 781:21-782:3. Thus, notwithstanding Rambjør's "isolated prior art disclosures," "the prior art as a whole . . . d[id] not teach away." *Gnosis*, 808 F.3d at 834.

c. Other potential advantages of DHA did not teach away from using purified EPA to avoid the rise in LDL-C.

785. Next, Plaintiffs argue that even if a skilled artisan had expected that purified EPA would not increase LDL-C, there was still no motivation to use purified EPA because the prior art suggested that DHA had advantages over EPA in improving other lipid markers that were believed to reduce cardiovascular risk—e.g., raising HDL-C, increasing LDL particle size, and reducing blood pressure. Among other references, Plaintiffs cite Mori, which highlighted some of these purported benefits of DHA. According to Plaintiffs, Mori expressed a preference for DHA overall, particularly its conclusion that DHA's ability to increase HDL-C (the so-called "good" cholesterol) and increase LDL particle size "may represent a more favorable lipid profile than that seen after EPA supplementation." DX 1538 at 8. Plaintiffs' argument is both legally and factually flawed.

786. Even assuming that Mori or other prior art taught a preference for DHA over EPA, the Federal Circuit has repeatedly held that "[a] reference does not teach away, however, if it merely expresses a general preference for an alternative invention." *Galderma*, 737 F.3d at 738 (reversing judgment of nonobviousness). The fact "that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (reversing judgment of nonobviousness). In other words, "the teaching away inquiry does not focus on whether a person of ordinary skill in the art would have merely *favored* one disclosed option over another disclosed option." *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017) (reversing judgment of nonobviousness). Where, as here, the prior art discloses two possibilities for formulating a product—here, EPA and DHA—"the fact that there may be reasons a skilled artisan would prefer one over the other does not amount to a teaching away from the lesser preferred but still workable option." *Id*.

787. Apart from the lack of teaching away, the fact that DHA may have had advantages over EPA does not diminish the motivation to use purified EPA to reduce triglycerides without raising LDL-C. Even if DHA were a better option, Federal Circuit precedent "does not require that the motivation be the *best* option, only that it be a *suitable* option." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014). In other words, Federal Circuit "case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). "[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Thus, even if the prior art taught that DHA had advantages over EPA unrelated to LDL-C levels (e.g., blood pressure, etc.), that would not alter the motivation discussed above to use purified EPA instead of a mixture of EPA and DHA to address LDL-C increases caused by Lovaza. *See also E.I. du Pont De Nemours & Co. v. MacDermid Printing Sols., L.L.C.*, 657 F. App'x 1004, 1014 (Fed. Cir. 2016) (for motivation, "the legally proper question is whether [the claimed solution] would be a suitable option in some respects, not necessarily in every respect."); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("[A] known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.").

788. In addition to being legally irrelevant, Plaintiffs' argument that DHA was preferred over EPA is unsupported by the record. If DHA were truly believed to have advantages over EPA for, then one would expect the pharmaceutical industry to develop purified DHA. Yet no such product has ever been developed. As Dr. Toth admitted, purified DHA "was just used investigationally" and never in any commercial or regulatory setting for reducing triglycerides or cardiovascular risk. Toth Tr. 1904:7-11. By contrast, Epadel *was* approved and commercialized in Japan as a triglyceride-lowering drug, and *was* used to reduce cardiovascular risk in the extensive and successful JELIS study. *Id*. at 1904:4-6 (Toth). This real-world evidence shows that a skilled artisan would have been highly motivated to develop purified EPA products not only for reducing triglycerides, but to reduce cardiovascular risk as well. Thus, the notion that a skilled artisan would

have preferred DHA over EPA is inconsistent with what actually happened in the prior art, which strongly suggests that EPA was preferred over DHA.

789. Plaintiffs' argument that a skilled artisan would have preferred DHA because of its effects on certain biomarkers is also inconsistent with ATP-III, which both sides relied on as authoritative. ATP-III made clear that lowering LDL-C was the "primary target" of therapy as of the priority date because "clinical trials robustly show[ed] that LDL-lowering therapy reduces risk for CHD [i.e., coronary heart disease]." DX 1526 (ATP-III Executive Summary) at 11; *see also* DX 1876 (ATP-III Final Report) at 14. By contrast, while HDL-C and LDL particle size might have been interesting factors to some artisans, there were no clinical trials confirming their significance on cardiovascular risk. ATP-III thus warned of "the possibility that therapeutic raising of HDL-cholesterol levels will not reduce CHD [i.e., coronary heart disease] risk as much as might be predicted from prospective epidemiological studies," and did "not recommend measurement of small LDL particles in routine practice." DX 1876 at 27, 39-40. To a skilled artisan, the purported benefits of DHA would not have taken precedence over EPA's more important ability to avoid an increase in LDL-C. Heinecke Tr. 792:8-794:17, 795:8-11.

790. Moreover, Dr. Toth admitted that the references he cited as reporting alleged benefits of DHA were all "based on biomarkers"—i.e., they were laboratory tests on parameters such as lipid levels that are used as theoretical predictors of cardiovascular risk. Toth Tr. 1903:18-1904:3. "None of those were outcome studies" that actually measured cardiovascular risk directly. *Id*. (Toth). By contrast, "JELIS was an outcome study," *id*., which did show real-world benefits of purified EPA in reducing cardiovascular risk. FF ¶¶ 349-358. There was no such evidence or outcome study for DHA. It is implausible, and Plaintiffs have cited no basis to believe, that a skilled artisan would place more weight on small biomarker studies showing *theoretical* advantages of DHA on cardiovascular health, than on a large-scale outcome study that showed *actual* advantages of EPA.

791. Plaintiffs' argument that a skilled artisan would not have used purified EPA because of alleged advantages of DHA thus lacks merit as a matter of both law and fact.

d. The possibility of other hypothetical options did not make the claimed method of treatment any less obvious to try.

792. Plaintiffs also challenge Defendants' alternative argument that the asserted claims were at least obvious to try. *See supra* Part III.C.1.b. Plaintiffs dispute that either purified EPA or the claimed dose of about 4 g/day were obvious to try. As with Plaintiffs' arguments against motivation and the reasonable expectation of success, these arguments fail both legally and factually.

793. First, Plaintiffs argue that purified EPA was not obvious to try because the prior art lacked "a finite number of identified, predictable solutions" to the problem of Lovaza increasing LDL-C. *See KSR*, 550 U.S. at 421. According to Dr. Toth, there was no "finite or limited number of potential options" because "[t]here could have been hundreds of options." Toth Tr. 1706:6-13. These options included "a new type of fibrate," "a new type of niacin," or even "[a]n entirely new type of triglyceride lowering agent." *Id*. at 1707:1-10 (Toth). Even focusing on fatty acids, Dr. Toth opined that the options were "potentially infinite" because "[y]ou could have varied the dose," "varied the ratio between the two principal omega-3s," or "add[ed] Omega-6s and Omega-9s." *Id*. at 1707:20-1708:3 (Toth). Dr. Toth's analysis, however, applies the wrong legal standard.

794. As the Federal Circuit has made clear, the question in an obvious-to-try case is not how many options are theoretically possible. After all, in almost every case, "the universe of potential [options] is theoretically unlimited." *In re Copaxone*, 906 F.3d at 1026. Instead, the inquiry focuses on which options already existed and "had clinical support in the prior art." *Id*.; *see also KSR*, 550 U.S. at 421 (focusing on the number of "identified" solutions). Dr. Toth's speculation about "entirely new type[s]" of drugs and "potentially infinite" doses is thus legally irrelevant.

795. The Federal Circuit has also made clear that the question of whether an invention was obvious to try cannot be assessed in a vacuum divorced from the prior art. As discussed above, a skilled artisan "would not have been required to try all possibilities in a field unreduced by the prior art." *Bayer*, 575 F.3d at 1350. Under Dr. Toth's own view that fibrates and niacin were already known to increase LDL-C in patients with severe hypertriglyceridemia, there was no reason for a skilled artisan to try "a new type of fibrate" or "a new type of niacin." Toth Tr. 1707:1-8. In fact, the list of existing triglyceride-lowering products that had not already been tried as a solution to the

problem of increased LDL-C was small. And to a skilled artisan facing the problem that Lovaza increased LDL-C, "[t]he prior art would have funneled the formulator toward the[] two options" of EPA and DHA, which were the two active ingredients in the drug. *Bayer*, 575 F.3d at 1350.

796. More generally, the mere fact "[t]hat the [prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (reversing judgment of nonobviousness). That is, "even if one possible obvious combination falls outside of the claims, it fails to undercut the fact that the other possible obvious combination lies within their scope." *See ACCO Brands Corp. v Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) (reversing judgment of nonobviousness). Thus, even if a skilled artisan might also have found it obvious to try other possible approaches, that would not have made the use of purified EPA, at a dose if about 4 g/day, any less obvious to try.

797. Second, Plaintiffs argue that real-world experience shows that it would not have been obvious to try purified EPA in patients with triglycerides of at least 500 mg/dL because, despite Epadel being available since 1991, there were no studies directed to using purified EPA in that population to reduce triglycerides without raising LDL-C. *See* ECF No. 327 at 20 (Plaintiffs' pretrial brief). This argument misconstrues both the relevant law and the facts in the record.

798. "Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004). As discussed below, there was no long-felt need here in view of the popular use of Lovaza with statins, and Plaintiffs did not assert or present any expert testimony on failure of others at trial. Thus, "the mere passage of time" since the introduction of Epadel "is not evidence of nonobviousness" for administering purified EPA to patients with severe hypertriglyceridemia. *Id.*

799. As a factual matter, this argument ignores that purified EPA (including Epadel) *was* administered to patients with triglycerides of at least 500 mg/dL. Again, Dr. Toth admitted that four prior-art references each had "at least one patient . . . with triglycerides over 500." Toth Tr. 1862:23-1863:1; FF ¶¶ 340-343. Likewise, Dr. Lavin admitted that "there must be at least one subject" with triglycerides above 500 mg/dL in Hayashi. Lavin Dep. Tr. 103:11-21. Moreover, individual patient

data in the Takaku study from 1991 showed that purified EPA successfully reduced triglycerides below 500 mg/dL in patients with severe hypertriglyceridemia. FF ¶ 295, 341; DX 1550 at 32; Heinecke Tr. 720:22-721:23. Thus, contrary to Plaintiffs' argument, skilled artisans not only tried, but succeeded in using purified EPA in patients with severe hypertriglyceridemia. And there is no evidence of any LDL-C increases in those patients.

800. The fact that these studies focused mostly on patients with triglycerides below 500 mg/dL does not mean that a study in patients with higher triglycerides was not obvious. The reason that studies on purified EPA lacked many patients with severe hypertriglyceridemia is not because researchers overlooked them, but because those patients are "rare"—particularly in Japan, where fish-based diets are prevalent. DX 1526 at 28 (ATP-III Executive Summary); Heinecke Tr. 798:16-22. Given the market size, it is not surprising that the pharmaceutical industry did not develop purified EPA as a treatment for severe hypertriglyceridemia earlier. In such "a niche market, it is not surprising that it took a few years for a company to expand on the prior art." *Tokyo Keiso Co. v. SMC Corp.*, 307 F. App'x 446, 453 (Fed. Cir. 2009).

801. Third, Plaintiffs argue that real-world facts show that about 4 g/day of purified EPA was not obvious to try because clinical trials continued to use various ratios of EPA and DHA instead of purifying either compound, as well as various doses besides 4 g/day. *See* Toth Tr. 1737:23-1739:4; PDX 6-9. All of these trials, however, were outcome trials focused on reducing cardiovascular risk—not reducing triglycerides in patients with severe hypertriglyceridemia. PDX 6-9 Indeed, Dr. Toth's opinion that skilled artisans "were varying the amount of EPA to DHA" and "varying the total dosage daily" was limited to the context of "find[ing] a better cardiovascular risk reducing agent." Toth Tr. 1738:21-1739:4. Even in that context, moreover, Dr. Toth cited no evidence that the researchers who designed these trials were deliberately varying the EPA:DHA ratio "to find a better" drug, as opposed to simply using different sources of fish oil. In any event, the mere fact that "possible obvious combination[s]" included some amount of DHA, or lower daily doses, for purposes of reducing cardiovascular risk, "fails to undercut the fact" that about 4 g/day of purified EPA was obvious for other reasons, such as reducing triglycerides without increasing LDL-C. *ACCO*, 813 F.3d at 1367.

802. Fourth, Plaintiffs argue that the prior art taught away from using a dose of about 4 g/day by suggesting that it could have adverse effects. Specifically, Dr. Toth cited an article by Nilsen, which found that 4 g/day of Lovaza did not reduce the risk of coronary events in patients who had recently suffered an acute myocardial infarction (i.e., a heart attack). PX 567 (Nilsen et al., *Effects of a High-Dose Concentrate of n-3 Fatty Acids or Corn Oil Introduced Early After an Acute Myocardial Infarction on Serum Triacylglycerol and HDL Cholesterol*, 74 Am. J. Clinical Nutrition 50 (2001) ("Nilsen")) at 1-2; Toth Tr. 1708:10-1710:23. Among the possible reasons that Lovaza failed to reduce cardiovascular risk, Nilsen speculated that it was "possible that the high doses of concentrated omega-3 fatty acids applied in this study exceeded some optimal threshold level, outweighing the beneficial effect, or even leading to an apparent adverse event." PX 567 (Nilsen) at 5. Plaintiffs' view that this statement in Nilsen taught away from trying a dose of about 4 g/day of purified EPA to reduce triglycerides is mistaken.

803. "Evidence concerning whether the prior art teaches away from a given invention must relate to and be commensurate in scope with the ultimate claims at issue." *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1381 (Fed. Cir. 2017). Here, the statement in Nilsen that Plaintiffs rely on does not relate to, and is not commensurate in scope with, the asserted claims, because (1) it involved the mixture of EPA and DHA in Lovaza, not the purified EPA required by the claims; and (2) it concerned whether 4 g/day of Lovaza reduced cardiovascular risk, not whether it reduced triglycerides, as the claims require. Thus, even if Nilsen's vague statement about a "possible" excess in dosing could teach away, it would not teach away from the claimed invention. At most, it would teach away from using a mixture of EPA and DHA to reduce cardiovascular risk, which has nothing to do with the claims. Indeed, it would be consistent with Nilsen to conclude that the problem with 4 g/day of Lovaza was the large amount of DHA in the dose, which a skilled artisan would be motivated to eliminate.

804. Moreover, the notion that the prior art taught away from a 4 g/day dose for lowering triglycerides, when 4 g/day was the dose approved by the FDA for that very purpose, is meritless. By definition, the fact that the FDA had approved that dose for Lovaza meant it was deemed both "safe" and "effective." 21 U.S.C. § 355(b)(1)(A). The mere fact that it was "possible" another dose

would be better for a different purpose does not show otherwise, and does not "criticize, discredit, or otherwise discourage" the use of about 4 g/day of purified EPA. *Galderma*, 737 F.3d at 739.

3. There are no secondary considerations that weigh against obviousness.

805. Before reaching a final conclusion of obviousness, any secondary considerations asserted by the patentee should be evaluated. "Evidence of secondary considerations, including evidence of unexpected results and commercial success, are . . . part of the totality of the evidence that is used to reach the ultimate conclusion of obviousness." *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (quotation omitted). "The existence of such evidence, however, does not control the obviousness determination." *Id*. In many cases, even "substantial evidence" of secondary considerations "do[es] not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious." *Id*.; *see also, e.g.*, *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018) (holding that "a strong showing of obviousness may stand even in the face of considerable evidence of secondary considerations"); *supra* ¶ 523 (collecting cases).

806. Although Defendants bear the ultimate burden of persuasion as to invalidity, "a patentee bears the burden of production with respect to evidence of secondary considerations of nonobviousness." *ZUP*, 896 F.3d at 1373. Here, Plaintiffs attempted to meet that burden with Dr. Toth's and Dr. Nicholson's testimony on four categories of secondary considerations:

- First, Plaintiffs assert that Vascepa's ability to reduce triglycerides without increasing LDL-C in patients with severe hypertriglyceridemia satisfied a long-felt and unmet need, was an unexpected result, and has been praised by the industry.
- Second, Plaintiffs assert that the reduction in cardiovascular risk observed in REDUCE-IT satisfied a long-felt and unmet need, was an unexpected result, overcame the skepticism of experts, and has been praised by the industry.
- Third, Plaintiffs assert that Vascepa's ability to reduce Apo B was an unexpected result.
- Fourth, Plaintiffs assert that Vascepa has been a commercial success.

807. With the exception of commercial success, Plaintiffs' alleged secondary considerations are based on the results of MARINE and REDUCE-IT—the clinical studies that Plaintiffs conducted to secure FDA approval for Vascepa. The reward mandated by Congress for a

clinical study, however, is not patent protection, but regulatory exclusivity. As provided in the Federal Food, Drug, and Cosmetic Act, applicants who submit "reports of new clinical investigations . . . essential to the approval of [a new drug] application" are rewarded with "three years" of regulatory exclusivity, during which no generic drug can be approved for the same indication. 21 U.S.C. § 355(j)(5)(F)(iii). No matter how useful and well-conducted those clinical studies may be, they cannot be the basis for patent protection if they merely confirm what was already known or expected based on the prior art. "Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007) (reversing jury verdict of nonobviousness).

808. For that reason and others explained below, none of the alleged secondary considerations that Plaintiffs assert weigh against obviousness. Plaintiffs' alleged secondary considerations are either unsupported by the record, lack the required nexus to the asserted claims, or both. Even assuming that Plaintiffs have provided some relevant evidence of secondary considerations, the asserted claims are nevertheless invalid as obvious in view of all four *Graham* factors.

a. The fact that Vascepa reduces triglycerides without raising LDL-C in most patients does not support the asserted claims.

i. There was no long-felt and unmet need to avoid LDL-C increases in patients with severe hypertriglyceridemia.

809. Plaintiffs have failed to produce probative evidence that there was a long-felt and unmet need to reduce triglycerides without increasing LDL-C in patients with severe hypertriglyceridemia. By definition, any long-felt need is not *unmet* if "others had previously solved the long-felt need." *In re PepperBall Techs., Inc.*, 469 F. App'x 878, 882 (Fed. Cir. 2012). Here, even assuming that there was, at some point, a long-felt need to avoid increases in LDL-C, any such need was previously met both by purified EPA and by combination therapy of Lovaza plus a statin.

810. First, for all the reasons discussed above, the purified EPA that was available in the prior art (e.g., Epadel) satisfied any need for lowering triglycerides without increasing LDL-C. As discussed, the prior art—including Mori, Hayashi, and Kurabayashi—showed that purified EPA did

not increase LDL-C, and a skilled artisan would have reasonably expected the same result in patients with triglycerides of at least 500 mg/dL. In fact, the prior art showed that purified EPA was administered to patients with triglycerides above that level, and there is no evidence that those patients experienced an increase in LDL-C. FF ¶ 305. Unlike the Lovaza label, which warned that Lovaza could increase LDL-C, the Epadel label contained no such warning. FF ¶ 305. Epadel's indication, moreover, included patients with severe hypertriglyceridemia—it was broadly indicated to treat "an excess of triglycerides," with no upper limit, and cited two studies that included patients with triglycerides above 500 mg/dL. *Supra* ¶ 749; FF ¶¶ 341-342. Thus, the purified EPA available in the prior art already met any alleged need to avoid increases in LDL-C. Heinecke Tr. 808:16-809:4.

811. The fact that purified EPA was not FDA-approved or commercially available in the United States does not change the result. Plaintiffs cannot argue that the asserted claims "met a long-felt but previously unsolved need, due to [Vascepa] being the first commercially available" EPA product in this country. *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017). "The fact that [Vascepa] was the first to receive FDA approval for commercial marketing does not overcome the fact that [purified EPA] compositions were already known." *Id*. at 1331; *see also AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 388 (D.N.J. 2015), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015) (finding that an alleged long-felt "need was satisfied by [a drug] available in Europe").

812. Indeed, given the lack of any material difference between Vascepa and Epadel, Plaintiffs cannot seriously contend that Vascepa satisfied a long-felt need that Epadel did not. As made clear by Dr. Eliot Brinton, who served on the REDUCE-IT steering committee, the products are materially identical: "Does Vascepa actually equal Epadel? They're both greater than 98 percent pure EPA ethyl ester. There's no known chemical difference between the two." DX 2106 at 217-19; Fisher Tr. 991:19-994:6. Plaintiffs' counsel agreed with Dr. Brinton's characterization on the record. Fisher Tr. 1050:7-14. "Where the differences between the prior art and the claimed invention are as minimal as they are here, [ ] it cannot be said that any long-felt need was unsolved." *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

813. Second, and independently, any need to lower triglycerides without increasing LDL-C was previously met by co-administering Lovaza with a statin. In fact, "as of March 2008, many

patients who took Lovaza were also given a statin to address the LDL-C increases." Toth Tr. 1822:12-14. Thus, "a skilled artisan, as of March 2008, would understand that if a patient is experiencing LDL-C increases because of Lovaza, a statin could be added." *Id.* at 1874:16-19 (Toth). And, "as of March 2008, it was known that Lovaza could be safely administered with statins." *Id.* at 1874:22-24 (Toth).

814. Similarly, Plaintiffs admitted in their validity contentions: "The rise in LDL-C was often offset by concurrent treatment with statins. The safety and efficacy of using prescription omega-3 [fatty acids] in combination with a statin has been well-established." DX 1953 at 18. Dr. Roger Blumenthal, the Director of the Johns Hopkins Ciccarone Center (Dr. Toth's employer), expressed a similar conclusion in the O'Riordan article, which Plaintiffs relied on as evidence of industry praise. As quoted in O'Riordan, Dr. Blumenthal "said that while LDL increases can occur with prescription fish oil or fibrates, the increase is 'modest' and 'not that big an issue.'" DX 1581 at 2. He pointed out that "the available prescription omega-3 fatty acid [i.e., Lovaza] is effective in reducing triglycerides, is well tolerated, and works well with statin therapy." *Id*. He also noted that "[m]ost patients with high triglycerides have mixed dyslipidemia and would likely be treated with background statin therapy." *Id*. As Plaintiffs' own contentions and Dr. Blumenthal's comments confirm, there was no long-felt and unmet need to avoid increases in LDL-C, because any such need was previously met by statins. Heinecke Tr. 809:18-810:14; *see also* Toth Tr. 1822:12-14.

815. To be clear, there was still a motivation to improve Lovaza to avoid LDL-C increases. "The fact that there is no long-felt, unmet need does not necessarily mean that there is no motivation to improve [the prior art]." *Celgene Corp. v. Peter*, 931 F.3d 1342, 1353 (Fed. Cir. 2019). Dr. Toth agreed that while "many patients who took Lovaza were also given a statin to address the LDL-C increases," "those patients would have to take two pills, the Lovaza and a statin," and "a skilled artisan would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases." Toth Tr. 1822:12-21; Heinecke Tr. 813:8-814:2. As discussed, the obvious "single pill" was purified EPA, which was not expected to raise LDL-C. And while a skilled artisan would have been *motivated* to develop that single pill to improve patient compliance, Plaintiffs

have cited no evidence of any long-felt *need* for that solution. In short, there was a "motivation to improve" Lovaza, but "no long-felt, unmet need" for the improvement. *Celgene*, 931 F.3d at 1353.

816. Even apart from the prior art's existing solutions, this is not a case where a long-felt and unmet need could suggest nonobviousness. As noted above, patients with severe hypertriglyceridemia are rare, so there was little commercial incentive to develop a new way to treat them. *Supra* ¶ 800.

817. This is evidenced by Lipitor, which is indicated "as an adjust to diet for the treatment of patients with elevated serum triglyceride levels, Frederickson Type IV." DX 3007 (2007 Lipitor label) at 14; *see also* DX 1986 (current Lipitor label); Toth Tr. 1813: 10-16. Frederickson Type IV includes some patients with severe hypertriglyceridemia. Toth Tr. 1813:17-19. In fact, "the median baseline triglyceride level [reported] in the LIPITOR label was 565" mg/dl. Toth Tr. 1817:22-24; *see also* DX 3007 at 12. Thus, Lipitor is indicated to treat elevated serum triglyceride levels in some patients with severe hypertriglyceridemia, but it is not marketed as such. Even Dr. Toth who is "familiar with Lipitor" and has probably "prescribed [it] thousands of times," was under the impression that Lipitor "had no indication to treat severe hypertriglyceridemia at all." Toth Tr. 1808:2-5, 1808:17-20. He stated that he was "not aware" that "Vascepa was not the first FDA-approved treatment shown to reduce triglycerides from above 500 . . . without increasing LDL-C." *Id.* at 1807:23-1808:1 (Toth). This is presumably because Lipitor "is primar[ily] used for cardiovascular risk reduction" rather than to treat severe hypertriglyceridemia. *Id.* at 1808:14-16 (Toth).

818. Evidence of "long-felt need" is not probative in such "a niche market, [where] it is not surprising that it took a few years for a company to expand on the prior art." *Tokyo Keiso*, 307 F. App'x at 453. For all these reasons, the fact that Vascepa does not increase LDL-C in most patients is not evidence that the claimed invention satisfied a long felt, unmet need.

ii. It was not "unexpected" that purified EPA would reduce triglycerides without raising LDL-C.

819. Vascepa's ability to reduce triglycerides without increasing LDL-C is also not an "unexpected result." For all the reasons discussed above, including the fact that there is no evidence

Epadel was associated with an LDL-C increase even though it had been used in patients with triglycerides above 500 mg/dL, a skilled artisan would have reasonably expected that purified EPA would reduce triglycerides without increasing LDL-C—including in patients with triglycerides of 500 mg/dL or higher. Thus, any alleged advantage of Vascepa in this regard is not relevant, because "by definition, any superior property must be *unexpected* to be considered as evidence of non-obviousness." *Pfizer*, 480 F.3d at 1371.

820. Even if it were "unexpected" that Vascepa would avoid increasing LDL-C in patients with triglycerides far *above* 500 mg/dL (e.g., 700-800 mg/dL), any such "showing of unexpected results is not commensurate in scope with the degree of protection sought by the claimed subject matter," which applies equally to patients with triglycerides of *exactly* 500 mg/dL. *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005). Again, for all the reasons discussed in Part III.C.1.a, it was at least reasonably expected that purified EPA would avoid increasing LDL-C in patients with triglycerides of exactly 500 mg/dL, which is enough to render all asserted claims obvious.

821. In opining otherwise, Dr. Toth cited public statements by Dr. Bays (the lead investigator of Plaintiffs' MARINE study) that the lack of increase in LDL-C was "surprising" and "unexpected." Toth Tr. 1720:4-16 (citing PX 833 at 6); *id*. at 1957:5-9 (citing DX 1741 at 7). But that was not an impartial assessment. Both of the articles that Dr. Toth cited were "supported" or "sponsored" by "Amarin Pharma, Inc.," and both disclosed that "Dr. Bays has received research grants and served as an advisor to Amarin." PX 833 at 1; DX 1741 at 1. These self-serving statements by Plaintiffs do not suggest any unexpected result. "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements [by the patentee] do[] not suffice." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

822. Privately, moreover, Dr. Bays did not agree with his Amarin-sponsored statement that the lack of increase in LDL-C was "unexpected." In an internal email sent before the MARINE publication was finalized, Dr. Bays pushed back on that characterization. In his words, the statement "that this finding was 'unexpected' is in contradiction to the rest of the manuscript" and "the reality of this drug development program." DX 1740 at 1. As discussed above, "the rest of the manuscript" suggests—consistent with Amarin's internal documents discussing its drug development program,

FF ¶¶ 371-397—that the lack of increase in LDL-C was expected: The article cites both Mori and Kurabayashi as "previous studies" showing that "although DHA treatment generally increased LDL cholesterol levels, EPA therapy did not." DX 1741 at 7, 9 (citing Mori); *see also id*. at 1, 9 (citing Kurabayashi). Plaintiffs' own conclusory, gratuitous characterization of this finding as "unexpected" later in the article thus fails to provide any probative evidence of nonobviousness.

iii. The industry did not praise Vascepa as LDL-C neutral.

823. For similar reasons, Plaintiffs failed to produce evidence of industry praise for the fact that Vascepa does not increase LDL-C. Dr. Toth cited several articles as purported evidence of such praise, but none of them support his opinion. Toth Tr. 1722:15-5, 1848:11-20.

824. First, Dr. Toth cited the O'Riordan article, which quoted several doctors on the results of MARINE. DX 1581. Specifically, Dr. Toth cited a statement by Dr. McGuire that "if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage," and a statement by Dr. Nissen that this "gives you all the benefit without the downside." *Id*. at 1-2; Toth Tr. 1606:24-1612:24. But as the article reveals, neither doctor gave unmitigated praise; both expressed caveats about those statements. Dr. McGuire "was cautious in interpreting the results" of MARINE, "insert[ed] a dose of caution," and made clear that his focus was on "cardiovascular effects," not just triglyceride reduction. DX 1581 at 1. If anything, Dr. McGuire saved his praise for "trials such as Japan EPA Lipid Intervention Study (JELIS)," which actually "showed a favorable signal of reduced cardiovascular events." *Id*. Similarly, Dr. Nissen "expressed the same caveats" about MARINE, and noted that he "would like to eventually see a head-to-head comparison between Lovaza" and Vascepa, which to date has never been done. *Id*. at 2.

825. Even apart from these caveats, Dr. Toth ignored the statement by Dr. Blumenthal, which O'Riordan also reported. As discussed above, Dr. Blumenthal did not praise Vascepa or MARINE, but instead dismissed MARINE's significance because typical increases in LDL-C with Lovaza were "'modest' and 'not that big an issue,'" especially since Lovaza "works well with statins." *Id*. at 2. Given these conflicting statements, O'Riordan as a whole does not suggest that Vascepa's ability to avoid increases in LDL-C has been praised by the industry.

826. Second, Dr. Toth relied on articles by Fialkow (PX 852) and Castaldo (PX 866). Toth Tr. 1612:25-1615:13. But those articles merely state the *fact* that Vascepa does not increase LDL-C—they do not *praise* Vascepa for that reason (or indeed, for any reason). The statement that Dr. Toth quoted from Fialkow states that "treatment with the EPA-only product, icosapent ethyl [i.e., Vascepa] has no LDL-C monitoring requirement." PX 852 at 5. Similarly, the statement that Dr. Toth quoted from Castaldo states that Vascepa "does not increase LDL-C levels, as supported by clinical studies and the icosapent ethyl product label." PX 866 at 6. These matter-of-fact observations, which merely repeat information from the Vascepa product label and the MARINE trial, do not praise Vascepa or the claimed invention. As the Federal Circuit has made clear, such "journal citations that reference the findings stated in [the patentee's] published efficacy studies . . . fall well short of demonstrating true industry praise." *Bayer*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

827. Third, Dr. Toth relied on the same Amarin-sponsored article discussed above in which Dr. Bays said that MARINE's results were "surprising." PX 833 at 6; Toth Tr. 1848:11-20. The Federal Circuit has made clear, however, that such "self-referential commendation [also] fall[s] well short of demonstrating true industry praise." *Bayer*, 713 F.3d at 1377; *see also In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016) (rejecting patentee's reliance on "self-serving statements from researchers about their own work" as alleged evidence of praise); *Geo. M. Martin*, 618 F.3d at 1305 (same—"self-serving statements" are not "industry praise").

828. In sum, Plaintiffs have not produced evidence that the industry "praised" the claimed invention for avoiding an increase in LDL-C. Even if such evidence existed, "industry praise of what was clearly rendered obvious by published references is not a persuasive secondary consideration." *Bayer*, 713 F.3d at 1377 (reversing judgment of nonobviousness).

b. The cardiovascular risk reduction observed in REDUCE-IT does not support the asserted claims.

829. Plaintiffs assert various secondary considerations based on REDUCE-IT, the clinical trial that led to Vascepa's recent approval for a new indication to reduce cardiovascular risk. Nothing about REDUCE-IT, however, supports the validity of the asserted claims. As shown below, REDUCE-IT lacks a nexus to the asserted claims, and is thus irrelevant to obviousness. In any event,

REDUCE-IT merely confirmed the results of the prior-art JELIS study, and thus reported nothing more than benefits of purified EPA that were already known and expected.

i. REDUCE-IT lacks a nexus to the asserted claims.

830. It is well established that "evidence of secondary considerations must have a 'nexus' to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (quotation omitted; vacating judgment of nonobviousness). To satisfy this requirement, any "evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (quotation omitted; reversing judgment of nonobviousness). "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis omitted). This is a threshold requirement before secondary considerations can be considered. Even "impressive" evidence of secondary considerations is not "entitled to weight" unless "it is relevant to the claims at issue." *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

831. "[T]he patentee" bears the "burden of production to demonstrate a nexus between the claimed [invention] and the secondary considerations." *MRC Innovations, Inc. v. Hunter Mfg., LLP*, 747 F.3d 1326, 1336 (Fed. Cir. 2014). There is "a rebuttable presumption of nexus between the asserted evidence of secondary considerations and a patent claim if the patentee shows that the asserted evidence is tied to a specific product and that the product *is* the invention disclosed and claimed." *Fox Factory*, 944 F.3d at 1373. But such a presumption applies only "when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them." *Id*. (quotations omitted).

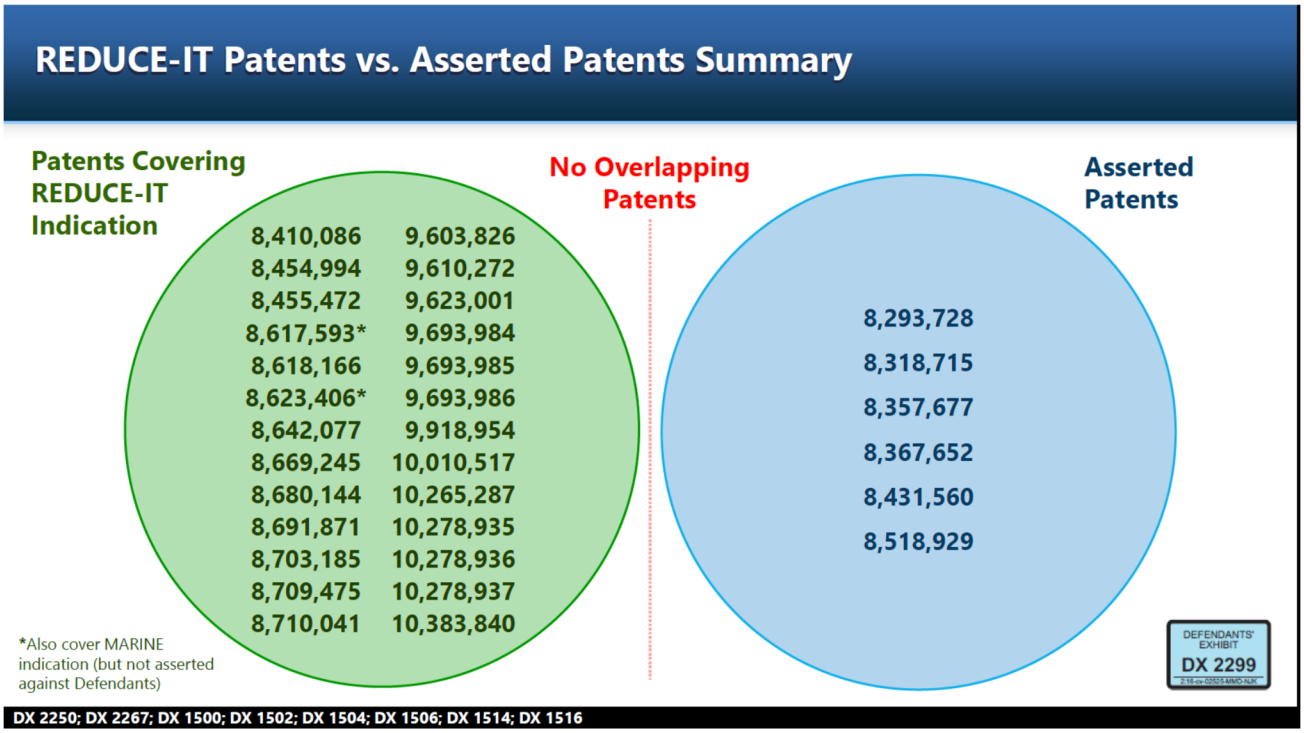
832. Here, Plaintiffs assert that they are entitled to a presumption of nexus for any evidence regarding Vascepa—including REDUCE-IT—because Vascepa allegedly embodies the asserted claims. As shown below, however, no nexus can be presumed because Vascepa also embodies *other* patents that are unrelated to the patents-in-suit. Thus, any benefits of Vascepa cannot be presumed to result from the asserted claims. In fact, Plaintiffs represented to the FDA that two dozen patents

cover Vascepa's new indication based on REDUCE-IT, but did not include any of the asserted patents in that disclosure. Regardless of any presumption, moreover, there is no nexus on the merits because REDUCE-IT fails to meet or match the scope of multiple claim limitations.

(1) Plaintiffs' unasserted patents on REDUCE-IT preclude any presumption of nexus, and confirm that the asserted patents do not relate to REDUCE-IT.

833. "Where a product embodies claims from two patents, a presumption of nexus can be appropriate only if the claims of both patents generally cover the same invention." *Fox Factory*, 944 F.3d at 1377. In other words, a "patentee [i]s not entitled to a presumption of nexus [where] the product embodie[s] at least two patented inventions." *Id*. at 1375. In that situation, "the burden [of production] thus remain[s] on the patentee to show that the product's success was due to the invention claimed in the patent asserted in the case." *Id*. (citing *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010), *vacated on other grounds*, 374 F. App'x 35 (Fed. Cir. 2010), *reinstated in relevant part*, 649 F.3d 1276 (Fed. Cir. 2011)).

834. Here, based on their representations to the FDA, Plaintiffs cannot dispute that Vascepa "embodie[s] at least two patented inventions." *Id*. When Plaintiffs filed their NDA for Vascepa's MARINE indication, and again when they filed their sNDA for Vascepa's REDUCE-IT indication, they were required to identify "each patent that claims the drug or a method of using the drug that is the subject of the NDA or amendment or supplement to it." 21 C.F.R. § 314.53(b). Plaintiffs submitted this "patent information" on FDA Form 3542a, which listed "each patent" that, in Plaintiffs' view, claimed "one or more methods of use for which approval is being sought." *See* DX 2250 at 1, 3. Thus, in identifying patents for their original NDA and recent sNDA, Plaintiffs "tied [the] patents either to the MARINE indication or to the REDUCE-IT indication." Ketchum Tr. 254:12-16. In total, Plaintiffs identified 46 patents, which are now listed in the FDA's "Orange Book" as patents that purportedly cover Vascepa. DX 2299. As shown below, however, none of the patents asserted in this case are among the patents that Plaintiffs identified as covering the REDUCE-IT indication. As Dr. Toth admitted, "Amarin has separate patents covering the method used in the REDUCE-IT study," and "those patents are not being asserted in this case." Toth Tr. 1895:4-10.



835. There is no dispute that these two groups of patents claim separate inventions. For example, one of the patents listed above on the left is U.S. Patent No. 10,278,936 (the "'936 patent"). DX 2001; Heinecke Tr. 817:17-818:5. Unlike the asserted patents, which claim priority to a provisional application filed in February 2009, the '936 patent claims priority to a provisional application filed more than two years later, in June 2012. *Id.* As a result, the '936 patent has a later expiration date—in June 2033, instead of the 2030 expiration date for all asserted patents. DX 2267 at 3. By definition, therefore, the invention claimed by the '936 patent must be patentably distinct from the asserted claims. If Plaintiffs' "later expiring patent [were] merely an obvious variation of an invention disclosed and claimed in [its earlier-expiring] patent, the later expiring patent [would be] invalid for obviousness-type double patenting." *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379 (Fed. Cir. 2014); *see also id.* at 1381 (different patents owned by the same entity but that expire at different times must be "patentably distinct").

836. Other differences confirm that the claimed invention and the invention claimed in Plaintiffs' REDUCE-IT patents are distinct. Unlike the asserted patents, which list five inventors, the '936 patent lists only one. DX 2001 at 1. The asserted patents are all titled, "Methods of Treating

Hypertriglyceridemia," whereas the '936 patent is titled, "Methods of Reducing the Risk of a Cardiovascular Event in a Subject on Statin Therapy." *Id.* And unlike the asserted claims, which each begin with the preamble, "A method of reducing triglycerides," the '936 patent's claims begin with, "A method of reducing risk of a cardiovascular event in a subject on statin therapy." *Id.* at 52-53. Moreover, while all asserted claims include the treatment of a patient with EPA for 12 weeks, the '936 patent's claims require treating the patient for "at least about 2 years." *Id.* In multiple ways, therefore, the invention claimed in Plaintiffs' Orange-Book patents listed for the REDUCE-IT indication differs materially from the invention claimed by the patents-in-suit.

837. That fact alone precludes any presumption of nexus between the benefits of Vascepa and the asserted claims. "This is not a situation where the success of a product can be attributed to a single patent, because [the Vascepa] product embodie[s] at least two [sets of] patents: the [asserted] patent[s] and [the REDUCE-IT] patent[s]. . . . As such, there is no presumption that the product's success was due only to the [claimed] patent." *Therasense*, 593 F.3d at 1299. "[T]he burden [of production] thus remain[s] on [Plaintiffs] to show that [Vascepa's] success [i]s due to the invention claimed in the patent[s] asserted in this case." *Fox Factory*, 944 F.3d at 1375.

838. Plaintiffs' Orange-Book listings, however, also preclude them from meeting that burden. Again, in submitting Form 3542a for the REDUCE-IT sNDA, Plaintiffs represented to the FDA that *only* the patents listed on the left-hand side above relate to Vascepa's REDUCE-IT indication. DX 2299. If Plaintiffs believed that the asserted patents claimed "a method of using [Vascepa] that is the subject of" the REDUCE-IT indication, they would have had to list those patents on the Form 3542a included with their sNDA. 21 C.F.R. § 314.53(b); *see* DX 2250. Yet Plaintiffs did not include any of the asserted patents in their patent listing for the REDUCE-IT indication. As shown above, there is no overlap between the patents listed for that indication and the asserted patents. DX 2299. Thus, Plaintiffs cannot assert that the asserted patents, which they listed only in connection with Vascepa's MARINE indication, also relate to the method of treatment in REDUCE-IT.

839. In short, based on Plaintiffs' Orange-Book patent listings alone, Plaintiffs are not entitled to a rebuttable presumption of nexus, and any presumption would be rebutted by Plaintiffs' own representations to the FDA that the asserted patents do not relate to REDUCE-IT.

(2) Regardless of any presumption, there is no nexus on the merits for multiple independent reasons.

840. Even apart from Plaintiffs' patent listings, and regardless of any presumption, there is no nexus between REDUCE-IT and the asserted claims. As noted above, "[i]t is the established rule that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Allergan*, 754 F.3d at 965 (quotation omitted; reversing judgment of nonobviousness). "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d at 1068 (emphasis omitted). For multiple reasons, Plaintiffs' evidence regarding REDUCE-IT does not satisfy these requirements.

841. First, REDUCE-IT lacks a nexus to the claimed use of Vascepa without a statin. As Dr. Toth admitted, "none [of] the asserted claims require a statin." Toth Tr. 1896:23-24. In fact, three claims expressly require treating a patient "who does not receive concurrent lipid altering therapy," and thus preclude using a statin. FF ¶ 180. In contrast, "all the patients in REDUCE-IT were taking statins"—"100 percent." Toth Tr. 1896:15-19; DX 1641 (Bhatt 2019) at 2. In fact, there is no dispute that a statin *must* be administered to reduce cardiovascular risk with Vascepa. As Dr. Toth testified, "it would have been unethical to have just a Vascepa monotherapy arm [in REDUCE-IT]. The FDA would never allow it because statin therapy is the standard of care." Toth Tr. 1897:5-10. This is reflected in the REDUCE-IT indication, which makes clear that Vascepa reduces cardiovascular risk only "as an adjunct to maximally tolerated statin therapy." DX 2248 (Vascepa Label) at 2.

842. Based on these undisputed facts, the REDUCE-IT results are not "commensurate in scope with the claims." *Allergan*, 754 F.3d at 965. For the three claims that exclude statins, the benefits of REDUCE-IT are entirely outside the scope of the claims. But even for the claims that are silent on statin use, there is no dispute that Vascepa can be, and often is, used without a statin in accordance with the claimed method. As Dr. Toth agreed, only "25 percent of the patients in MARINE were taking statins." Toth Tr. 1896:20-22. At most, therefore, the REDUCE-IT results could only be relevant to that subset of patients. But the asserted claims are much broader—they

include the 75% of patients in MARINE who took Vascepa without a statin. Because the REDUCE-IT results are "not commensurate with the full scope of the patent's claims," they "lack[] a nexus with the scope of the [asserted] patent[s'] claimed invention." *Allergan*, 754 F.3d at 965.

843. Put differently, the benefits in REDUCE-IT "actually result[ed] from something other than" the claimed invention, which at least allows using Vascepa without a statin. *In re Huai-Hung Kao*, 639 F.3d at 1068. Instead, the benefits resulted from a *different* invention—one claimed in Plaintiffs' unasserted patents—which *requires* using a statin. DX 2001 ('936 pat.) at 1, 52-53. REDUCE-IT thus lacks a nexus to the asserted claims. Heinecke Tr. 821:2-18.

844. Second, REDUCE-IT lacks a nexus to the claimed use of Vascepa for 12 weeks. All of the asserted claims include the use of Vascepa for only about 12 weeks. For example, as Plaintiffs have argued, the MARINE study described in the label was an infringing use of Vascepa that lasted exactly 12 weeks. FF ¶ 161. By contrast, REDUCE-IT lasted for almost five years. DX 1641 at 1. The reported benefits did not even begin to occur until after a full year, and were not statistically significant until after two years. *Id*. at 5, Fig. 1; Heinecke Tr. 819:17-820:12. Thus, Dr. Toth "didn't offer any opinion that REDUCE-IT showed any cardiovascular benefit . . . as of 12 weeks." Toth Tr. 1895:14-19. He agreed that "if you stop [Vascepa] at four months, then you're going to lose that benefit." *Id*. at 1896:6-14. That is fatal to any alleged nexus. Because the REDUCE-IT results took two years to manifest, they are "not commensurate with the full scope of the patent's claims," which includes treatment durations as short as 12 weeks. *Allergan*, 754 F.3d at 965.

845. Third, REDUCE-IT lacks a nexus to the claimed use of EPA to reduce triglycerides. As Dr. Toth conceded, "none of the patent claims at issue in this case have a limitation with regard to reducing cardiovascular risk." Toth Tr. 1894:15-18. Instead, all asserted claims are directed to "[a] method of reducing triglycerides." The benefits in REDUCE-IT, however, were unrelated to reducing triglycerides. According to the REDUCE-IT publication (Bhatt), "the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur *irrespective of the attained triglyceride level* at 1 year (≥150 or <150 mg per deciliter), which suggests that the *cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level*." DX 1641 at 10 (emphasis added). The authors concluded that their "observations

suggest that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events than that with placebo may be explained by metabolic effects *other than a reduction of triglyceride levels*." *Id*. (emphasis added). In other words, the REDUCE-IT benefits "actually result[ed] from something other than" the claimed method of reducing triglycerides, which precludes any finding of nexus. *In re Huai-Hung Kao*, 639 F.3d at 1068; Heinecke Tr. 816:8-817:12; Fisher Tr. 1035:4-1037:2.

846. On cross-examination, Plaintiffs argued that "the Bhatt article doesn't rule out TG lowering as responsible for at least part of the CV benefit." Fisher Tr. 1119:11-14. But that is not the relevant inquiry. Because there is no presumption of nexus, as discussed above, Plaintiffs bear the "burden of production to demonstrate a nexus between the claimed [invention] and the secondary considerations." *MRC Innovations*, 747 F.3d at 1336. Plaintiffs have not produced any evidence that the benefits in REDUCE-IT resulted from lowering triglycerides. On the contrary, the evidence of record, including Bhatt, suggests the opposite. Thus, there is no basis to conclude that the REDUCE-IT results have a nexus to the claimed method of reducing triglycerides.

847. Fourth, REDUCE-IT lacks a nexus to avoiding an increase in LDL-C, which is a limitation of all but two asserted claims, and is the purported discovery that allegedly distinguishes the asserted claims from the prior art. According to the Bhatt article, the REDUCE-IT investigators "found no substantial difference in the benefit of icosapent ethyl as compared with placebo with respect to the primary end point according to whether the patients who received placebo had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels." DX 1641 at 7. Thus, the REDUCE-IT benefits "actually result[ed] from something other than" the claimed method of avoiding an increase in LDL-C, as required by eight of the asserted claims. *In re Huai-Hung Kao*, 639 F.3d at 1068; Heinecke Tr. 820:13-821:1.

848. Fifth, the REDUCE-IT results are not commensurate in scope with the claims because the results were limited to patients with multiple cardiovascular risk factors that the asserted claims do not require. As explained in Bhatt, REDUCE-IT was limited to patients who "were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional risk factor." DX 1641 at 2. Likewise, the REDUCE-IT

indication is limited to patients with "established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." DX 2248 (Vascepa Label) at 2.

849. By contrast, the asserted claims do not contain any of these limitations. As Dr. Toth admitted, "aside from severe high triglycerides, there's no other risk factor[] required by the patents related to cardiovascular issues." Toth Tr. 1894:22-25. For example, none of the claims are limited to patients with diabetes. Heinecke Tr. 826:10-12; Fisher Tr. 1093:21-22. Moreover, there is no dispute that many patients with severe hypertriglyceridemia do not have risk factors such as diabetes. For example, in MARINE, only 28% of patients were diabetic. DX 1741 (Bays 2011) at 2; Heinecke Tr. 825:22-826:9. The asserted claims cover the treatment of the remaining patients who were not diabetic, as well as patients who more generally do not have two or more cardiovascular risk factors. Because the REDUCE-IT results are limited to patients with such risk factors, they are "not commensurate with the full scope of the patent's claims." *Allergan*, 754 F.3d at 965.

850. Sixth, REDUCE-IT lacks a nexus to the limitation in all asserted claims that patients must have triglycerides of at least 500 mg/dL. As Dr. Toth admitted, "REDUCE-IT focused on patients with triglycerides below 500." Toth Tr. 1894:12-14. According to Bhatt, "[e]ligible patients had a fasting triglyceride level of 150 to 499 mg per deciliter," which means that patients with triglyceride of at least 500 mg/dL were not eligible to participate. DX 1641 at 2. The benefits in REDUCE-IT thus "actually result[ed] from something other than" the claimed invention, which is limited to treating patients with triglycerides of at least 500 mg/dL, so "there is no nexus" as a matter of law. *In re Huai-Hung Kao*, 639 F.3d at 1068; Heinecke Tr. 818:12-819:16.

851. Indeed, because REDUCE-IT focused on patients with triglycerides below 500 mg/dL, conducting REDUCE-IT did not even infringe the asserted claims. In analogous circumstances, the Federal Circuit has held that evidence regarding products that are not covered by the asserted claims cannot be relevant to secondary considerations. The same principle applies to the method claims here: Because the asserted claims do not cover the REDUCE-IT, evidence regarding REDUCE-IT is irrelevant. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 n.42 (Fed. Cir. 1985) (if "products were not covered by the [asserted] patents, [ ] then the secondary considerations [based on those products] would not have had any relevance to the

obviousness/nonobviousness determination"); *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1366 (Fed. Cir. 2001) (secondary considerations based on "copying Amazon's '1-Click®' feature is legally irrelevant unless the '1-Click®' feature is shown to be an embodiment of the claims").

852. Plaintiffs have argued that some patients in REDUCE-IT developed higher triglyceride levels after they became eligible for the study, and thus the study did include a handful of patients with triglycerides of at least 500 mg/dL. *See* ECF No. 331 ¶ 963. This argument, however, only confirms that severe hypertriglyceridemia is not a chronic or purely genetic condition, as Plaintiffs contend for infringement purposes. In any event, Plaintiffs' argument contradicts their position that Defendants' prior-art references are not relevant unless all patients in the study had triglycerides of at least 500 mg/dL. Plaintiffs cannot have it both ways. If studies in which no patients, or only a handful of patients, had triglycerides of at least 500 mg/dL are irrelevant, then so is REDUCE-IT.

853. In sum, for multiple independent reasons, the REDUCE-IT results are not commensurate in scope with, and did not actually result from practicing, any of the asserted claims. Thus, regardless of whether any rebuttable presumption of nexus applies, there is no nexus on the merits between REDUCE-IT and the asserted claims. As a result, evidence concerning REDUCE-IT is not relevant to determining whether the asserted claims are invalid as obvious.

ii. The claimed invention did not meet any alleged long-felt need, and any such need was previously met by JELIS.

854. For the same reasons that the asserted claims lack a nexus to REDUCE-IT, Plaintiffs have failed to produce evidence that the claims satisfied a long-felt and unmet need to reduce cardiovascular risk. "Once a long-felt need is established, evidence must show that the claimed invention satisfied that need." *In re Gardner*, 449 F. App'x 914, 918 (Fed. Cir. 2011). Here, there is no evidence that "the claimed invention" satisfied any alleged need to reduce cardiovascular risk. For example, as discussed above, REDUCE-IT provides no evidence that administering purified EPA to a patient for 12 weeks without a statin—a method within the scope of all asserted claims—has any effect on cardiovascular risk. At most, the benefits in REDUCE-IT are attributable to purified EPA

itself, which was available in the prior art—not the claimed method of treatment. In similar circumstances, courts have rejected the alleged satisfaction of a long-felt need where "the benefits touted by [the patentee] were attributable to the compound itself rather than the [claimed] method of treatment." *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1102 (Fed. Cir. 2015). Because REDUCE-IT does not "show that *the* [*asserted*] *patent*[*s*] met any such 'need'" to reduce cardiovascular risk, Plaintiffs have "fail[ed] to show . . . a long-felt, unmet need *alleviated by the patent*[*s*]." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009) (emphasis added).

855. Regardless of whether the claimed method reduces cardiovascular risk, evidence of a long-felt need is not relevant if "others had previously solved the long-felt need." *In re PepperBall*, 469 F. App'x at 882. Here, as discussed in the findings of fact above, the prior-art JELIS study showed that Epadel previously satisfied any need to reduce cardiovascular risk in statin-treated patients. FF ¶¶ 348-359. The product tested in JELIS was the "EPADEL Capsule," which was commercially available on "the Japanese market" and contained "highly (>98% purified EPA)." DX 1552 (Yokoyama 2003) at 3-4; Heinecke Tr. 743:9-22. JELIS followed more than 18,000 statin-treated patients, about half of whom were taking Epadel daily, for almost five years. DX 1553 (Yokoyama 2007) at 1. By the end of the study, patients taking Epadel with a statin had a statistically significant, "19% relative reduction in major coronary events" compared to patients taking a statin alone. *Id*. Based on that reduction, the JELIS investigators concluded that "EPA is a promising treatment for prevention of major coronary events." *Id*.; Heinecke Tr. 749:3-750:5, 821:22-822:20.

856. The reduction in cardiovascular events in JELIS was even more pronounced in patients with elevated triglycerides. The WO '118 application, which was published in December 2007, reported a "partial analysis of the results obtained in JELIS" (i.e., a sub-analysis) "for patients having the risk factors of a triglyceride (TG) of at least 150 mg/dL and a HDL-C of less than 40 mg/dL." DX 1524 at 39, 13-14. In that subgroup of patients, "the rate of suppression of the cardiovascular event occurrence . . . was 53%"—more than twice as high as the 19% reduction in the patient general population. *Id*. at 45-46, 2; Toth Tr. 11923:1-1924:13. The same sub-analysis was later formally published in Saito 2008. DX 1547 at 1, 5. Thus, as shown by Yokoyama 2007 and

WO '118, and later reconfirmed by Saito 2008, any long-felt need to reduce cardiovascular risk in statin-treated patients—including patients with elevated triglycerides—was previously met by Epadel.

857. Plaintiffs cannot seriously dispute these results. JELIS was published in *The Lancet*, "a top medical journal" with "a very strong reputation in the medical community" and a "rigorous" peer-review process. Toth Tr. 1899:20-1900:8. Indeed, Dr. Toth himself is "a peer reviewer" for *The Lancet*. *Id*. While Plaintiffs and Dr. Toth criticized JELIS at trial, they previously praised JELIS as showing exactly what they now contend was first proven by REDUCE-IT. FF ¶¶ 375, 378-382, 389-405. For example, Plaintiffs represented to the FDA that "JELIS was a very large, well-designed study with blinded endpoint evaluation that demonstrated a statistically significant reduction in CV risk due to statin add-on therapy." DX 1836 (Formal Dispute Resolution Request) at 71. At the time, Plaintiffs insisted that JELIS's "results should not be dismissed lightly," and that the evidence "strongly support[ed] the consideration of the JELIS study results in evaluating the potential CV benefits of Vascepa therapy." *Id*. at 71, 81. Likewise, in their marketing documents, Plaintiffs emphasized that sales representatives should "leverage the JELIS data as reduction in CV events with EPA is a compelling part of the Vascepa story." PX 583 at 6. Dr. Ketchum also presented JELIS as a "CV outcomes study of EPA" that was "well designed." DX 1838 at 9. Even as recently as the FDA's 2019 Advisory Committee meeting, Plaintiffs represented that JELIS "reported a CV benefit with EPA consistent with REDUCE-IT." DX 2235 at 70. Similarly, Dr. Toth himself previously called JELIS "a nice Japanese study" that showed "a whopping 53% reduction in risk." DX 1709 at 16-17.

858. Dr. Toth and Dr. Ketchum admitted that these previous statements were accurate and did not overstate the results of JELIS. Ketchum Tr. 232:15-18; Toth Tr. 1909:6-13. Indeed, Dr. Toth admitted that he "personally ha[s] praised the JELIS trial as demonstrating that the addition of EPA to ongoing statin therapy incurred benefit." Toth Tr. 1912:1-6. Plaintiffs' other experts and researchers have also praised JELIS. In 2017, for example, Dr. Budoff called JELIS "a positive trial" for cardiovascular risk reduction. DX 2139 at 10. In 2013, Dr. Ballantyne (the lead investigator of ANCHOR) said that "JELIS showed that EPA might be a good new option in treating patients with

elevated TGs[,] especially since it did not elevate the LDL C." PX 833 at 6. And Dr. Bays (the lead investigator of MARINE) said that "JELIS is the only trial ever performed in which a lipid altering drug was shown to provide CV outcome benefits in patients already taking statins." *Id*.

859. Nevertheless, Plaintiffs and Dr. Toth attempted to undermine JELIS at trial by calling into question the reliability of its results. All of their criticisms, however, are directly contrary to their previous representations—including Plaintiffs' representations to the FDA.

860. First, Plaintiffs argue that LDL-C levels were not well controlled in JELIS because the doses of statins were too low. ECF No. 331 ¶ 931. Dr. Toth's "beef with [JELIS] is that the statins were profoundly underdosed," which he alleged was "a big problem." Toth Tr. 1924:25-1925:3. In 2014, however, Plaintiffs represented the exact opposite to the FDA. At the time, Plaintiffs argued that "LDL-C was adequately controlled for a majority of JELIS patients." DX 1836 (Formal Dispute Resolution Request) at 73. Plaintiffs specifically rejected "the contention that LDL-C levels were not well controlled" in JELIS, or that the study was flawed for using "a low dose of statins." *Id*. at 70, 73. Instead, Plaintiffs insisted that "[t]he statin therapy in JELIS followed Japanese Atherosclerosis Society (JAS) guidelines." *Id*. As they explained, "while baseline LDL-C levels in JELIS were somewhat high," those levels quickly dropped once the study was underway: "After initiation of statin therapy at randomization, a 25% reduction in LDL-C was observed," which "would likely meet the JAS LDL-C goal for a majority of JELIS patients." *Id*. Plaintiffs concluded that "the JELIS patients were on a dose of pravastatin that is recognized as adequate to treat LDL-C according to contemporary Japanese- and United States-based guidelines." *Id*. In other words: "Patients in JELIS were treated according to JAS guidelines, including appropriate reductions in LDL-C that appear to have met LDL-C goals." *Id*. at 81. Plaintiffs' litigation arguments about the dosing of statins and purportedly elevated LDL-C levels in JELIS cannot be reconciled with their previous representations to the FDA, which Plaintiffs' Chief Scientific Officer, Dr. Ketchum, admitted were "a truthful and accurate characterization of JELIS." Ketchum Tr. 232:15-18.

861. Similarly, in other documents, both Plaintiffs and Dr. Toth characterized JELIS as a study on statin-treated patients—with no mention of any concerns with the dosing of statins or the resulting LDL-C levels. *See, e.g.*, DX 1709 at 16-17 (Dr. Toth describing "nice" JELIS study "in

which all the participants were on background statin therapy"); DX 3009 at 3 (Dr. Toth contending that "there is support from the JELIS trial" that "the addition of EPA to ongoing statin therapy, particularly in patients with triglycerides over 150, incurred benefit"); DX 1829 at 6 (Plaintiffs: JELIS showed risk reduction for patients given EPA "in combination with a statin versus treatment with statin alone"); *id*. at 10 (Plaintiffs noting that all patients in JELIS were "given statins"); DX 1816 at 81 (Plaintiffs noting that all patients in JELIS were "on background statin . . . as first-line therapy"); DX 2252 at 63 (Plaintiffs noting that "JELIS evaluated an ethyl-EPA preparation similar to Vascepa, administered as an adjunct to statin therapy"). As Dr. Toth admitted, he previously "characterized the JELIS trial as demonstrating that the addition of EPA to statin therapy incurred cardiovascular benefit." Toth Tr. 1914:6-10. None of these previous descriptions of JELIS questioned the dosing of statins or the level of LDL-C treatment. Plaintiffs' litigation-inspired arguments to undermine JELIS are inconsistent with their previous representations (including to their regulator and investors), and thus not credible.

862. Second, because JELIS was conducted in a Japanese population, Plaintiffs argue that its results cannot be extrapolated to Westerners. ECF No. 331 ¶ 932. In particular, Dr. Toth speculated that since a typical Japanese diet includes more fish than a Western diet, and fish contains both EPA and DHA, the JELIS results might be attributed to higher doses of both EPA and DHA, not EPA alone. Toth Tr. 1763:9-1764:16. Again, however, Plaintiffs' litigation argument that the JELIS results on EPA do not translate to a Western population directly contradict their previous representations to the FDA. In 2014, Plaintiffs rejected the notion that the "JELIS results [are] not [ ] applicable to a United States-based non-Japanese population." DX 1836 (Formal Dispute Resolution Request) at 70. On the contrary, Plaintiffs argued that "results from CV studies conducted in an exclusively Japanese population are applicable to the United States population." *Id*. at 71. Plaintiffs noted that the U.S.-based ACC/AHA guidelines relied on a major cardiovascular outcomes trial on pravastatin, "[d]espite being conducted in an exclusively Japanese population." *Id*. at 71-72. Thus, "there is a precedent set by the ACC/AHA for applying results from an exclusively Japanese population to a United States-based population." *Id*. at 81. Plaintiffs further noted that, if anything, the higher fish consumption in Japan justified the use of a higher dose of EPA (4 g/day): "if a

threshold EPA level is needed for therapeutic effects, higher doses of EPA likely need to be considered in populations where fish consumption is lower than observed in Japan." *Id*. at 72. Again, Plaintiffs' current positions cannot be squared with their previous representations to the FDA, which were admittedly accurate.

863. Regardless, even if the benefits in JELIS were limited to Japanese patients or patients who consume large quantities of fish, those limitations would not be relevant to the asserted claims, which include the treatment of such patients. There is no limitation in any asserted claim that requires the treated "subject" to be a Westerner, or that restricts the subject's diet. This is in contrast to multiple *unasserted* claims that require the treated subject to "consume a Western diet"—for example, claim 15 of the '728 patent, which depends from asserted claim 1. DX 1500 ('728 patent) claim 15. "As [the Federal Circuit] has frequently stated, the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004). "In such a setting, . . . the doctrine of claim differentiation is at its strongest." *Id*. Thus, in light of the unasserted dependent claims that are limited to patients consuming a "Western diet," there is a strong presumption that the asserted claims are *not* so limited—and instead include patients who consume a typical Japanese diet. Thus, even if REDUCE-IT were the first study to show that EPA reduces cardiovascular risk in patients with a Western diet, the fact remains that JELIS previously showed the same result in patients with a Japanese diet, whose treatment is within the scope of all asserted claims.

864. Third, Plaintiffs criticize JELIS's "open-label" (i.e., unblinded) design, because the cardiovascular event that drove the finding of statistical significance—unstable angina—was purportedly subjective and could be influenced by bias. ECF No. 331 ¶¶ 933-40. According to Dr. Toth, "it's up to the physician evaluating the patient as to whether or not they're going to diagnose unstable angina. But if you know that they are or are not on therapy, that could influence your decision to call it one way or the other." Toth Tr. 1753:2-19. Dr. Toth contrasted this alleged flaw with REDUCE-IT, which was placebo-controlled and showed statistical significance for endpoints that were more objective, such as cardiovascular death. *E.g.*, Toth Tr. 1772:5-5-1773:14.

865. Once again, Plaintiffs' prior representations contradict this argument. In their 2014 submission to the FDA, Plaintiffs rejected the criticism that "JELIS was an open label trial, which could influence patient and physician behavior in reporting symptoms." DX 1836 (Formal Dispute Resolution Request) at 71. Plaintiffs insisted that while JELIS "was open-label, this however does not negate its findings." *Id*. As they explained, "JELIS was a controlled trial with a PROBE design (prospective, randomized open-label, blinded endpoint evaluation) that randomized 18,645 patients," and thus was "a very large, well-designed study with blinded endpoint evaluation." *Id*. Likewise, in an earlier FDA submission in 2008, Plaintiffs emphasized that "all endpoints and severe adverse events [in JELIS] were reviewed and adjudicated in a blinded fashion by an end-point committee." DX 1816 at 81 (IND June 2008 package). Tellingly, despite discussing JELIS extensively before this case began, neither Plaintiffs nor Dr. Toth questioned JELIS's open-label design, or its reliance on unstable angina as a "subjective" endpoint, until this litigation. Instead, like other commentators, they accepted JELIS's peer-reviewed "PROBE" design, which ensured that endpoints were adjudicated in a blinded fashion and minimized the potential for bias. Fisher Tr. 994:10-995:21.

866. The fact that JELIS was not placebo-controlled, or did not show statistical significance for the same individual endpoints as REDUCE-IT, does not diminish its value. There is "no authority from the Supreme Court or [the Federal Circuit] requiring as a matter of law, for reasonableness of an expectation of success, testing of specific doses versus placebo that shows the relevant result with statistical significance." *Acorda*, 903 F.3d at 1333. On the contrary, skilled artisans "*can* draw reasonable inferences about the likelihood of success even without a perfectly designed clinical trial showing a statistically significant difference." *Id*. at 1334.

867. At bottom, Plaintiffs' argument is that REDUCE-IT was a *better* study than JELIS, because only REDUCE-IT led to Vascepa's FDA approval to reduce cardiovascular risk. But the fact that REDUCE-IT "was the first [study] to receive FDA approval" for reducing cardiovascular risk with EPA "does not overcome the fact that [JELIS's benefits] were already known." *Novartis AG*, 853 F.3d at 1330. Nor is it relevant that the FDA did not accept JELIS as definitive proof that Vascepa would reduce cardiovascular risk. The Federal Circuit has repeatedly "reject[ed] [any] attempt to equate regulatory compliance with evidence of nonobviousness." *AstraZeneca*, 603 F.

App'x at 1003. Because the FDA applies a much more rigorous standard than the "reasonable expectation of success" that applies in patent law, difficulties in receiving FDA approval "are not particularly probative with respect to obviousness." *Allergan*, 726 F.3d at 1292.

868. Likewise, the fact that Plaintiffs needed to conduct REDUCE-IT despite the existence of JELIS "does not imply lack of awareness of the likely result; rather, studies are frequently conducted to confirm what is suspected to be true. An incentive to conduct a confirmatory study frequently exists even when one has every reason to expect success." *Soft Gel Techs., Inc. v. Jarrow Formulas, Inc.*, 864 F.3d 1334, 1342 (Fed. Cir. 2017). For that reason, "[s]cientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *PharmaStem*, 491 F.3d at 1363-64 (reversing jury verdict of nonobviousness).

869. Plaintiffs cannot seriously dispute that REDUCE-IT was "a confirmatory study" for JELIS. The REDUCE-IT investigators themselves noted that JELIS "led to the design of" REDUCE-IT. DX 1641 (Bhatt 2019) at 2; Heinecke Tr. 823:1-14. Likewise, in the recent Advisory Committee meeting, Plaintiffs represented that JELIS "reported a CV benefit with EPA *consistent with* REDUCE-IT." DX 2235 at 70 (emphasis added). Dr. Brinton, who was on the committee and was a co-author of the Bhatt paper, stated that his "rationale for approving the expanded indication for Vascepa is basically the clinical trial evidence for JELIS," which REDUCE-IT merely confirmed. DX 2106 at 217-19; Fisher Tr. 992:8-995:21. Likewise, Dr. Budoff told interviewers in 2017 that "overall, [the] Jelis Trial [sic] was positive," and based on JELIS he believed that REDUCE-IT "will be a positive trial" as well. DX 2139 at 10; Fisher Tr. 1006:10-1008:25. In fact, before any of the REDUCE-IT results were available, Dr. Budoff estimated that REDUCE-IT had an "85% chance of success." DX 2140 at 15. Thus, the fact that REDUCE-IT was necessary for Plaintiffs to obtain FDA approval of their sNDA does not make it any less of a confirmatory trial.

870. Moreover, to the extent FDA approval is relevant, the FDA did not accept REDUCE-IT as evidence that Vascepa reduces the risk of cardiovascular death. When Plaintiffs submitted their sNDA, they sought an indication "to reduce the risk of *cardiovascular death*, myocardial infarction, stroke, coronary revascularization, and unstable angina." DX 2247 (Vascepa Proposed Label) at 2 (emphasis added). The FDA, however, rejected that request, and approved Vascepa "to reduce the

risk of myocardial infarction, stroke, coronary revascularization, and unstable angina"—i.e., every cardiovascular outcome that Plaintiffs requested *except* death. DX 2248 (Vascepa Label) at 2. Thus, contrary to Plaintiffs' contentions, the FDA did not find that REDUCE-IT demonstrated a reduction in cardiovascular death, let alone a reduction that differentiated the study from JELIS.

871. For all these reasons, the asserted claims did not meet a long-felt need to reduce cardiovascular risk in statin-treated patients, let alone a need that was not previously met by JELIS.

iii. It was not unexpected that combination therapy with purified EPA and statins would reduce cardiovascular risk.

872. For essentially the same reasons, the fact that purified EPA reduces cardiovascular risk in statin-treated patients is not an "unexpected result." On the contrary, Yokoyama 2007 reported that combination therapy with purified EPA and a statin resulted in "a 19% relative reduction in major coronary events," and concluded that "EPA is a promising treatment for prevention of major coronary events." DX 1553 at 1. As discussed in the previous section on long-felt need, Plaintiffs' and Dr. Toth's criticisms of JELIS are unfounded, especially given their prior inconsistent statements.

873. Even assuming that REDUCE-IT showed a greater benefit than JELIS, that would not mean that its results weigh against obviousness. "Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art." *Galderma*, 737 F.3d at 739. For example, differences "measured by percentages, reflect a difference in degree, not in kind." *Id*. Here, the overall results of REDUCE-IT and JELIS differ only be degree—i.e., by percentages. Both studies were designed to evaluate essentially the same primary composite endpoint, which tallied major cardiovascular events. *See* DX 1641 (Bhatt 2019) at 9; DX 1553 (Yokoyama 2007) at 1; Heinecke Tr. 822:13-17. JELIS found an overall 19% reduction in cardiovascular events, whereas REDUCE-IT found a 25% reduction. *Id*. In both studies, the reductions were statistically significant. *Id*. That reflects a mere difference in degree, not in kind. Heinecke Tr. 822:21-25. If anything, JELIS ultimately found a greater reduction in risk. As reported in WO '118 and Saito 2008, patients in JELIS with elevated triglycerides had a 53% reduction in risk—more than twice as high as REDUCE-IT's 25% reduction. DX 1524 (WO '118) at 45-46, 2; DX 1547 (Saito 2008) at 1, 5.

874. Nevertheless, Dr. Toth contended at trial that REDUCE-IT showed "a profound difference in kind" because it was the first to report statistical significance for individual objective endpoints, such as cardiovascular death. Toth Tr. 1773:2-14. But again, there is no requirement for "a perfectly designed clinical trial showing a statistically significant difference" to "draw reasonable inferences about the likelihood of success." *Acorda*, 903 F.3d at 1333. And in any event, the FDA *rejected* REDUCE-IT as evidence that EPA reduces cardiovascular death. FF ¶ 421.

875. Dr. Toth also cited evidence that a number of clinical trials on omega-3 fatty acids failed before REDUCE-IT. PDX 6-29. But those studies involved *mixtures* of EPA and DHA. *Id*. None of them evaluated purified EPA, and none involved patients with severe hypertriglyceridemia. Toth Tr. 1899:3-7. Moreover, while the "failed" studies that Dr. Toth cites were *initiated* before March 2008, none of them were actually completed and published until at least 2010. PDX 6-29. Until that time, including as of the priority date (i.e., March 2008 or February 2009), there was no reason to believe that any of these studies would fail. As Dr. Toth admitted, "as of March 2008," and "even in 2009, a skilled artisan wouldn't know that any of these studies were going to fail." Toth Tr. 1898:20-1899:2. On the contrary, "the fact that there were eight cardiovascular studies, as of March 2008, and as of 2009, showed that there were high expectations that fish oil would have cardiovascular benefits." *Id*. at 1898:12-16 (Toth); *see also In re Montgomery*, 677 F.3d 1375, 1382-83 (Fed. Cir. 2012) (the "initiat[ion] [of] human clinical trials for a therapeutic product or process . . . is reasonably predictive," even before "actual results" are obtained (quotation omitted)).

876. The fact that the studies would later go on to fail is irrelevant to whether success was expected as of the priority date. The relevant inquiry is whether the "evidence of unexpected results . . . would not have been expected by one of ordinary skill in the art *at the time of the invention*." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (emphasis added); *see also id*. at 974 (rejecting the patentee's argument that a prior-art drug "was discovered to be toxic" after the priority date because, at the time, it was "not yet known to have high toxicity," and thus the lack of toxicity in similar drugs was not unexpected (quotation omitted)).

877. Even if Vascepa's ability to reduce cardiovascular risk were unexpected, it would not be a relevant result that weighs against obviousness. As with other secondary considerations, a

"showing of unexpected results [that] is not commensurate in scope with the degree of protection sought by the claimed subject matter" is not probative. *In re Harris*, 409 F.3d at 1344. For all the reasons discussed above, the lack of nexus between the REDUCE-IT results and the asserted claims precludes Plaintiffs from relying on those results to support the claims.

878. More specifically, any unexpected result in REDUCE-IT does not support an inference that the asserted claims were nonobvious. Logically, "for an unexpected property of an invention to be evidence of non-obviousness it must have been contemplated as a goal of the inventive process. The fact that the hypothetical person of ordinary skill would have been surprised to learn that the particular combination of elements created an unexpected benefit completely unrelated to the desired outcome does not logically imply that it would not have been obvious to combine those elements to achieve the desired result." *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 667 (D.N.J. 2006). In *Pfizer*, for example, the patented invention was embodied by the drug Celebrex, which was developed as an "NSAID [i.e., non-steroidal anti-inflammatory drug] with reduced gastrointestinal side effects." *Id*. In defending the patent's validity, the patentee relied on the drug's "superior cardiovascular properties" as evidence of "unexpected results." *Id*. The court, however, rejected the evidence as irrelevant because it "was not contemplated as a goal of the inventive process." *Id*. As the court explained: "The fact that a person of ordinary skill would have been surprised by the cardiovascular properties of Celebrex does not imply that it was not obvious to create this compound to produce an NSAID with reduced gastrointestinal side effects. Thus, this unexpected result does not suggest non-obviousness of the invention and is not relevant to the obviousness inquiry."

879. This case presents a similar situation. Here, as discussed in Part III.C.1.b., the claimed method of administering purified EPA would have been obvious, or at least obvious to try, to a skilled artisan who was attempting to reduce triglycerides in patients with severe hypertriglyceridemia without raising LDL-C. "The fact that a person of ordinary skill would have been surprised by the cardiovascular properties of" purified EPA, however, "does not imply that it was not obvious" to use the drug for the entirely different purpose of treating severe hypertriglyceridemia. *Id*.

880. In any event, as with other secondary considerations, "an unexpected result or property does not by itself support a finding of nonobviousness." *Bristol-Myers*, 752 F.3d at 976. Even if the REDUCE-IT results were unexpected, they are "not . . . sufficient to outweigh the other evidence of obviousness" presented above. *Allergan*, 726 F.3d at 1293; *see also Richardson-Vicks*, 122 F.3d at 1484 (overturning jury verdict of nonobviousness and holding that "unexpected results . . . , although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious").

iv. There was no relevant skepticism as of the priority date.

881. Plaintiffs also produced no probative evidence that experts as of the priority date were skeptical that purified EPA would reduce cardiovascular risk. At trial, Dr. Toth only cited articles on EPA-DHA mixtures—not purified EPA—that were all published after the relevant 2008-2009 timeframe. Specifically, Dr. Toth cited the 2018 Cochrane meta-analysis (PX 953), the 2018 Aung article (PX 954), and the 2018 Feuerstein article (PX 951). Toth Tr. 1766:2-1768:25. All of these articles concerned omega-3 fatty acids mixtures (e.g., fish oil supplements or Lovaza), and all were published about a decade after the alleged priority date of March 2008.

882. As with unexpected results, evidence post-dating the invention is not relevant to skepticism. Rather, the Federal Circuit has only "consider[ed] skepticism or disbelief *before the invention* as an indicator of nonobviousness." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000) (citation omitted; emphasis added); *see also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (noting that "objective evidence of nonobviousness includes . . . skepticism of skilled artisans *before the invention*" (emphasis added)); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (secondary considerations include "[t]he skepticism of an expert, expressed *before these inventors proved him wrong*" (emphasis added)). Post-priority skepticism is irrelevant to whether the claimed invention would have been obvious as of the priority date.

883. Moreover, contemporaneous evidence on or around the priority date did not show skepticism, but instead showed enthusiasm for using omega-3 fatty acids to reduce cardiovascular risk. Again, Dr. Toth admitted that "as of March 2008, and as of 2009, . . . there were high expectations that fish oil would have cardiovascular benefits." Toth Tr. 1898:12-16. In fact,

Plaintiffs' IND submission to the FDA in June 2008 represented that "a large body of evidence has accumulated showing that regular intake of omega-3 fatty acids exerts cardioprotective effects in both primary and secondary coronary heart disease prevention." DX 1816 at 59. Plaintiffs explained that "[t]his mounting body of evidence has led the American Heart Association to recommend the consumption of omega-3 fatty acids in the form of fish or in capsule form at a dose of lg/day for secondary prevention of cardiovascular (CV) disease . . . and this recommendation has now been included in ACC/ AHA guidelines for the long-term management of patients with stable angina and acute coronary syndromes." *Id*. While this enthusiasm was not necessarily unanimous, the "lack of enthusiasm by a few is not equivalent to skepticism or failure of others such that [a claimed invention] would not have been obvious." *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019).

884. Even after the priority date, experts including Dr. Toth continued to express enthusiasm, not skepticism, about the promise of omega-3 fatty acids to reduce cardiovascular risk. In 2010, Dr. Toth wrote that "[t]he cardiovascular benefits of omega-3 fatty acids (i.e., 'fish oils'; [EPA] and [DHA]) are well documented." DX 3020 at 12. In fact, Dr. Toth was enthusiastic about *all* lipid-lowering therapies, including fibrates, niacin, and other therapies that he characterized at trial as "failures." Toth Tr. 1730:12-1732:24. As Dr. Toth explained in his 2010 article: "The use of lipid-lowering therapies to reduce the risk of cardiovascular morbidity and mortality has been intensively studied," and "[t]here is strong evidence to support the use of statins, fibrates, niacin, BAS [i.e., bile acid secretants] and fish oils." *Id*. at 20. For example, "[t]he combination of statins with niacin and fish oils has been studied prospectively in the HATS and JELIS trials, respectively. These combinations are effective and provide incremental benefit beyond statin monotherapy." *Id*.

885. In 2015—still four years before REDUCE-IT—Dr. Toth continued to express enthusiasm about the ability of omega-3 fatty acids and other lipid-lowering drugs to reduce cardiovascular risk. In an interview with Dr. Bays, Dr. Toth agreed that there was "clinical trial evidence that administering omega-3 fatty acids reduced atherosclerotic cardiovascular events." DX 1709 at 16-17. Dr. Toth relied not only on JELIS (which he praised as a "nice Japanese study"), but also on GISSI—"an important study done in the late 1990s," which showed that "purified omega-3

fish oil in patients who were post an acute coronary syndrome showed remarkable reductions in risk of reinfarction and cardiovascular mortality." *Id*. at 17. Based on this evidence, Dr. Bays and Dr. Toth agreed that "omega 3 fatty acids were actually the first lipid-altering drug added to a statin shown to reduce atherosclerotic risk." *Id*. at 18. Their enthusiasm for omega-3 fatty acids based on JELIS and GISSI was also echoed by Dr. McGuire, whom Plaintiffs quoted for purposes of alleging industry praise regarding LDL-C. As reported in O'Riordan in 2010, Dr. McGuire found that "trials such as Japan EPA Lipid Intervention Study (JELIS) and GISSI-Prevenzione showed a favorable signal of reduced cardiovascular events among patients treated with fish oil." DX 1581 at 1.

886. Dr. Toth's testimony at trial was also inconsistent with his previous praise for fibrates. At trial, he compared fibrates to EPA, and characterized them as having "failed" to reduce cardiovascular risk. Toth Tr. 1731:14-22. Back in 2015, however, Dr. Toth expressed a different opinion: "Looking at subgroup analyses from those trials, in the group with high triglycerides and low HDL, do fibrates incur benefit? The answer, consistently, is that they do. All the fibrate studies suggest that fibrate therapy in patients with triglyceride levels higher than 200 mg/dl and HDL levels typically lower than 40 or 35 mg/dl provides a reduction in cardiovascular event rates. In the FIELD study the reduction was 27%, in the BIP trial it was 41%, and in the HHS, there was an outsize benefit of approximately 70% in a primary prevention population of younger men." *Id*. at 13. As recently as 2018, Dr. Toth continued to opine that "[t]he fibrate trials do consistently demonstrate benefit in patients in the subgroup with high triglycerides and low HDL." DX 3009 at 3.

887. In sum, there was no skepticism about whether purified EPA would reduce cardiovascular risk in statin-treated patients as of the priority date. On the contrary, there was widespread enthusiasm that not only purified EPA, but omega-3 fatty acids in general and even other lipid-lowering drugs would reduce such risk. Even after the priority date, experts including Dr. Toth continued to express the same enthusiasm. The fact that some trials eventually failed, and that meta-analyses reported those negative results a decade after the priority date, are not relevant to whether skilled artisans were skeptical at the relevant time (let alone to whether skilled artisans were skeptical about the claimed invention, which has nothing to do with reducing cardiovascular risk).

v. Praise for REDUCE-IT is legally irrelevant.

888. Although REDUCE-IT has received praise in recent months, Plaintiffs failed to produce evidence that this praise is relevant to the asserted claims. As with other secondary considerations, "[i]ndustry praise must also be linked to the patented invention" in order to be considered. *Geo. M. Martin*, 618 F.3d at 1305. Thus, the Federal Circuit has discounted even "exceptional praise [from] the industry press," which was "indeed impressive," where the patentee has "not shown that it is relevant to the claims at issue and thus entitled to weight." *Paulsen*, 30 F.3d at 1482; *see also, e.g.*, *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (affirming judgment of obviousness where, "[w]hile the evidence shows that the overall system drew praise . . . , there was no evidence that the success of the commercial embodiment of the [ ] patent was attributable to the . . . material difference between [the prior art] and the patented invention.").

889. Here, for all the reasons discussed above regarding the lack of nexus between REDUCE-IT and the asserted claims, any praise for REDUCE-IT is irrelevant to whether the claimed invention—a method of reducing triglycerides in patients with severe hypertriglyceridemia—would have been obvious to a skilled artisan as of the priority date.

890. Again, moreover, any praise for REDUCE-IT is praise for a *confirmatory* study, which merely proved what skilled artisans already believed based on JELIS. "The problem with that evidence is that there was no indication that the praise for [REDUCE-IT] was based on any inventive contribution [the investigators] made, as opposed to their proof" of what was expected. *PharmaStem*, 491 F.3d at 1365. "As noted, the former is a basis for patentability; the latter is not." *Id*.

c. Reduction in Apo B is not an unexpected result.

891. For the same reasons discussed above in Part III.C.3.a.ii., there is no basis to conclude that Vascepa's ability to reduce Apo B in most patients is an "unexpected result." During prosecution, and again briefly at trial, Plaintiffs relied on the 8.5% reduction in Apo B relative to placebo that was shown in MARINE. DX 1591 (notice of allowance) at 10; Toth Tr. 1724:1-4. While the examiner accepted Plaintiffs' argument that the reduction in Apo B was unexpected, he overlooked (and Plaintiffs did not point out) prior art that expressly showed this result.

892. Again, Kurabayashi showed that patients treated with 96.5% purified EPA for 48 weeks experienced a reduction in Apo B by 6.9%. DX 1534 at 5. As measured by "one-way repeated-measures analysis of variance" (a statistical method that examines trends in data over time), the reduction in Apo B for EPA-treated patients was highly statistically significant, with a p-value of less than 0.001. *Id.*; Heinecke Tr. 737:3-23. Any difference between the 6.9% reduction shown in Kurabayashi and the 8.5% reduction in MARINE is not a difference "in kind," but "merely in degree," and thus is not "probative of nonobviousness." *Galderma*, 737 F.3d at 739; Heinecke Tr. 806:17-20. In fact, while the 8.5% reduction in MARINE was statistically significant, Dr. Sheinberg testified that it "is absolutely not clinically significant." Sheinberg Tr. 643:22-25.

893. At trial, Dr. Toth criticized Kurabayashi because it did not test EPA alone, but instead administered estriol to all patients in the study. Toth Tr. 1663:9-1664:10. As Dr. Heinecke explained, however, estriol was used as the study's "control"—as expressly stated in the reference, DX 1534 (Kurabayashi) at 2—and the control group taking estriol alone had no significant decrease in Apo B. Heinecke Tr. 737:24-738:8; DX 1534 at 5. Given the highly significant reduction in Apo B with EPA, and the lack of any reduction with estriol alone, a skilled artisan would have reasonably expected that EPA was responsible for the effect. *Id.* Indeed, there was no reason to believe that EPA and estriol interacted to produce that result. In fact, Kurabayashi suggested the opposite. The study showed that estriol increased triglycerides, whereas EPA reduced them. Thus, the two compounds were antagonistic, nor synergistic. Heinecke Tr. 735:21-736:9.

894. A skilled artisan also would have read Kurabayashi in conjunction with Nozaki and Grimsgaard, both of which tested purified EPA and showed a statistically significant reduction in Apo B. Heinecke Tr. 738:9-17; DX 1541 (Nozaki 1992) at 4; DX 1530 (Grimsgaard 1997) at 5. Neither of these studies administered estriol, and thus both supported a reasonable expectation that purified EPA alone would reduce Apo B. Heinecke Tr. 738:18-25. Moreover, Grimsgaard showed a 3% reduction in Apo B, which is also a mere difference in degree from MARINE's 8.5% reduction. Heinecke Tr. 809:17-24. Thus, based on the prior art, the reduction in Apo B seen in MARINE was not an unexpected result that weighs against nonobviousness.

d. Vascepa is not a relevant commercial success.

895. Plaintiffs have failed to produce probative evidence that Vascepa is a relevant commercial success.

896. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck*, 395 F.3d at 1376. This "rationale has no force in this case." *Id.* Instead, Vascepa has generated annual and cumulative losses through December 2018. FF ¶ 435. Vascepa has "only been able to garner a small single digit percentage of about 3 percent [market share] in the marketplace" for the period 2013 through November 2018. FF ¶ 439. Similarly, "Vascepa has only been able to garner on a cumulative basis about 4.5 million prescriptions compared to the other triglyceride-lowering products" which have totaled 161 million prescriptions. FF ¶ 439. This very small market share for Vascepa is not indicative of a product that's been a commercial success or a marketplace success. Hofmann Tr. 1223:20-1224:5; *id.* at 1233:12-20.

897. Amarin's net present value calculations based upon ten years of third party forecasts are inherently speculative based upon Amarin's and the forecasters(s) own admissions. FF ¶¶ 437-438.

898. Given the cumulative loses and small market share associated with Vascepa, a person skilled in the art would not have been financially motivated to bring a Vascepa-like product to market. *See, e.g.*, *Merck*, 395 F.3d at 1376. Thus, Plaintiffs' "evidence" of commercial success fails to support a finding of non-obviousness.

899. Furthermore, as with other secondary considerations, "for commercial success to be probative evidence of nonobviousness, a nexus must be shown between the claimed invention and the evidence of commercial success." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012). Here, any purported evidence of commercial success is not tied to the asserted claims.

900. First, the "vast majority" of Vascepa cumulative sales from 2013 through 2018 fail to practice the asserted claims of the Patents-in-Suit. FF ¶ 440. Specifically, from 2013 through 2018, "about three-quarters of the prescriptions are off-label" (as such, only approximately one quarter of

the sales of Vascepa® purportedly practice the asserted claims of the Patents-in-Suit). *Id.* Therefore, any purported evidence of commercial success based on the number of sales or prescriptions lacks a nexus to the patents-in-suit."

901. Second, the performance of Vascepa® is primarily due to Amarin's marketing efforts. Where other "factors [a]re identified as contributing to . . . commercial success, including marketing efforts," such success "does not alter the obviousness analysis." *Wm. Wrigley Jr.*, 683 F.3d at 1363. That is precisely the case here. Amarin has utilized many forms of marketing and promotional efforts for Vascepa®, including detailing, utilizing a co-marketing partner, high share of voice ("SOV"), and sampling. FF ¶¶ 441-444. From 2013 through 2018, Amarin spent approximately $575 million in marketing and sales expense and generated only $698 million in cumulative net sales, which represents 82 percent of sales over a six-year period from launch. *Id.* Pricing incentives, such as co-pay programs for patients and discounts and rebates to third party payers, and product sampling have also been used to drive the performance of Vascepa®. FF ¶¶ 446-447.

902. Tellingly, Vascepa® has the highest promotional dollar spend for TG reducing brand products, yet has achieved only a three percent prescription share. FF ¶ 439.

903. "[W]hen you look at the significance of the discounts, rebates and other incentives, and consider them alongside the marketing and promotion, and the fact that there is not – most of the prescriptions are being written for patients that aren't even covered by the patents, these are strong, strong indicators of a lack of nexus between the marketplace performance of Vascepa, which isn't even all that good, but shows a lack of nexus to the marketplace performance in the claims of the patents-in-suit." Hofmann Tr. 1282:2-10.

904. Third, there are dozens of patents that are listed in the Orange Book as covering Vascepa. Hofmann Tr. 1287:2-8. Only six of those patents are the patents-in-suit. It is improper to attribute the entire sales and marketplace performance of Vascepa to the six patents-in-suit. "[B]y taking credit for the entirety of the marketplace performance of Vascepa and tying that or claiming it to these six patents that are at issue here, without ascribing any value or even considering all these other patents that Amarin has told FDA and told the world that they believe cover the product, you get an economically unsound result where you could theoretically take credit for a hundred percent

of the sales for the patents-in-suit here, and then take credit for those same sales associated with patents that aren't even involved in this case." *Id.* at 1288:8-18 (Hofmann).

905. Because the "evidence [produced by Plaintiffs] does not show that the success of [Vascepa] [i]s directly attributable [to the asserted claims]," it is appropriate and necessary to "discount[] the evidence of commercial success as a secondary consideration rebutting [the] showing that the claimed invention would have been obvious." *Wm. Wrigley Jr.*, 683 F.3d at 1364.

* * *

906. For the reasons discussed above, in view of all four *Graham* factors (including alleged secondary considerations), Defendants have proven by clear and convincing evidence that all 10 asserted claims are invalid as obvious under 35 U.S.C. § 103(a).

D. Defendants do not infringe the three claims that exclude concurrent lipid-altering therapy, and the remaining seven claims were at least obvious to try because adding a statin would be reasonably expected to achieve the claimed effects.

907. As a third, independent basis to grant judgment for Defendants, the three asserted claims that require treating a patient who does "not receive concurrent lipid altering therapy"—i.e., '728 patent claims 1 and 16, and '715 patent claim 14—are not infringed because Defendants' labels do not instruct doctors against administering such therapy. The remaining seven claims, which allow concurrent lipid altering therapy, are invalid because it was at least obvious to try administering purified EPA with a statin, which was reasonably expected to achieve all claimed lipid effects.

1. Defendants' labels do not induce infringement of the three claims that exclude concurrent lipid altering therapy.

908. For the three asserted claims that require treating a patient without concurrent lipid altering therapy, nothing in Defendants' labels "instructs users to perform the patented method," as required to induce infringement. *Grunenthal*, 919 F.3d at 1339.

909. At the outset, there is no dispute that administering Defendants' products *with* a concurrent lipid altering therapy, such as a statin, is a substantial noninfringing use. As reported in the Clinical Studies section of Defendants' labels, 25% of patients in the MARINE trial took statins. FF ¶ 185. The treatment of at least those patients did not infringe the asserted claims that exclude concurrent lipid altering therapy. Thus, because Defendants' products have "substantial

noninfringing uses, intent to induce infringement cannot be inferred." *Horizon*, 940 F.3d at 702. Instead, to prove inducement, Plaintiffs bear the burden of proving that the labeling actually "instructs"—i.e., "requires"—doctors *not* to use a statin or other concurrent lipid altering therapy. *Id*.

910. Plaintiffs have not met that burden. The only alleged instruction that Plaintiffs have pointed to is the statement in the Clinical Studies section that "twenty-five percent of patients were on concomitant statin therapy." ECF No. 327 at 17. According to Plaintiffs, this statement "indicat[es] to clinicians that 75% of the study subjects were administered the drug as a *monotherapy*, i.e., without any concurrent additional lipid-altering therapy." *Id*. That theory, however, was discredited by Plaintiffs' clinical infringement expert at trial, and is flawed as a matter of law.

911. As Dr. Budoff admitted, "a statin is an *example* of a lipid-altering therapy," but many other drugs are also concurrent lipid altering therapies, including fibrates, niacin, and ezetimibe. Budoff Tr. 520:13-25 (emphasis added). Although the Clinical Studies section reports that 25% of patients were on concomitant statin therapy, it is silent about other lipid altering therapies. Thus, even assuming that the remaining 75% of patients were not taking statins, Dr. Budoff conceded that "the labeling doesn't say anything about whether this 75 percent of patients were taking a different lipid-altering therapy." *Id*. at 522:22-25. Indeed, it would be entirely consistent with the labelling to conclude that *all* patients were on *some* type of concurrent lipid altering therapy. The premise of Plaintiffs' infringement theory—that the labelling "indicat[es] to clinicians that 75% of the study subjects were administered the drug . . . without any concurrent additional lipid-altering therapy"—is thus factually wrong. ECF No. 327 at 17; Sheinberg Tr. 647:13-16.

912. As a result, the labelling as a whole does not even *describe* the use of purified EPA without concurrent lipid altering therapy, much less specifically *encourage* that use. The only statements that even relate to other lipid altering therapies simply note that they *can* be added—e.g., in the Clinical Studies section and the Clinical Pharmacology section, which notes the absence of "Drug-Drug Interactions" between EPA and atorvastatin. FF ¶¶ 187-188. Without even a description of an infringing use in Defendants' labels, Plaintiffs cannot meet their burden to show that the labelling "instructs users to perform the patented method." *Grunenthal*, 919 F.3d at 1339.

913. Even if Plaintiffs were correct that the labelling describes using the drug "without any concurrent additional lipid-altering therapy" (it does not), that premise would still be insufficient to find inducement—as a matter of law. Again, "[m]erely describing the infringing use, or knowing of the possibility of infringement, will not suffice; specific intent and action to induce infringement must be shown." *Horizon*, 940 F.3d at 702. If "the label does not require" the patented use that is described, it "does not encourage infringement." *Id*. That principle applies even where the approved use of the drug "includes" the patented use, which is not enough to prove inducement unless the label "specifically encourage[s]" that use over others. *Grunenthal*, 919 F.3d at 1339.

914. Here, it is undisputed that the labelling does not "require" or "specifically encourage" using EPA without concurrent lipid altering therapy. As Dr. Budoff admitted, the statement in the Clinical Studies section "is just letting doctors know that 25 percent of patients in the clinical study discussed in the labeling were taking a statin." Budoff Tr. 521:23-522:1. That statement "is not an instruction to doctors to make sure they use a statin," and "it's not mandating not to use a statin either." *Id*. at 522:5-9 (Budoff). Far from encouraging doctors to refrain from using concurrent lipid altering therapy, Dr. Budoff conceded that "there's nothing in the . . . label as a whole suggesting any preference for using icosapent with or without a statin." *Id*. at 523:7-13. Instead, he admitted that "defendants' labeling leaves it entirely up to the physician's discretion as to whether to add a concurrent lipid-altering therapy to icosapent." *Id*. at 523:21-25. These admissions are dispositive. Because "the label does not require" (*Horizon*, 940 F.3d at 701) and "do[es] not specifically encourage" (*Grunenthal*, 919 F.3d at 1339) the infringing use, there is no inducement.

915. *Horizon*, which also involved a concurrent therapy, is on point. As discussed above, the claimed method in *Horizon* required both "apply[ing] the inventive formulation" to treat osteoarthritis *and* "apply[ing] sunscreen, insect repellant, or a second topical medication." 940 F.3d at 702. The defendant's label described the application of both products. It instructed users to apply the indicated drug (i.e., "the inventive formulation" in the claims) and then warned patients to "wait until the treated area is dry before applying a second topical agent, such as sunscreen, insect repellant, or covering the area with clothing." *Id*. at 686 (quotation and alteration omitted). Even though the label expressly described the use of both products as required by the claimed method, the Federal

Circuit found no inducement. It was not enough that the "labeling tracks closely with the asserted claims." *Id*. at 701. Because the accused drug label "only *require*[*d*] the first step of this method," and did "not *require* subsequent application of sunscreen, insect repellant, or a second medication," the label did "not encourage infringement." *Id*. at 702 (emphasis added).

916. The only difference here is that, instead of requiring the use of a second medication (as in *Horizon*), the claimed method in this case requires *not* using a second medication. The logic of *Horizon*, however, applies either way. As in *Horizon*, there are two relevant steps to the claimed method: administering purified EPA, and *not* administering a concurrent lipid altering therapy. Defendants' labels, however, "only require the first step"—i.e., administering purified EPA. *Id*. They do "not require" a doctor to refrain from administering the second medication that is excluded by the claims. As in *Horizon*, that second medication is optional, and the labelling expresses no preference on whether to add it. Thus, the labelling "does not encourage infringement." *Id*.

917. There is also no basis to find infringement under an "inevitable inducement" standard. Unlike in *AstraZeneca*, where explicit instructions "would *necessarily* lead patients to use" the drug in an infringing manner, here there is no instruction that "would necessarily lead" a doctor to prescribe EPA without a statin. 633 F.3d at 1061 (emphasis added). Nor is this case like *Eli Lilly*, where "instructions [we]re unambiguous on their face and encourage[d] or recommend[ed] infringement" to at least some physicians. 845 F.3d at 1369. Because there are no such instructions here, let alone "unambiguous" instructions, there is no basis to conclude that "the product labeling that Defendants seek would inevitably lead some physicians to infringe." *Id*.

918. The only case that Plaintiffs have cited to support their theory is *Sanofi*, but that case is inapposite. According to Plaintiffs, *Sanofi* stands for the rule that when "a product label describes that a drug is safe and effective for both monotherapy and combination therapy, that label encourages, recommends, or suggests *both*." ECF No. 327 at 16-17. But this reading of *Sanofi* is far too broad. As discussed, the Indications and Usage section of the label in *Sanofi* "sa[id] that [the drug] is indicated for use in certain patients and *refer*[*red*] *to section 14 on 'Clinical Studies'* for identification of those patients." *Sanofi II*, 875 F.3d at 643 (emphasis added). That reference was critical to the finding of infringement. As the Federal Circuit explained: "The reference to the Clinical Studies

section [ ] of the label *expressly directs* the reader to that section for elaboration of the class of patients for whom the drug is indicated." *Id*. at 645 (emphasis added). It was only based on that explicit reference to the Clinical Studies section in the Indications and Usage section that the Federal Circuit found induced infringement of the claimed combination therapy.

919. By contrast, here there is no instruction that directs physicians to the Clinical Studies section. The Indications and Usage section does not mention the Clinical Studies section at all, and is entirely silent as to whether patients should receive concurrent lipid altering therapy. While the indicated use "includes" treating patients without concurrent lipid altering therapy, "it also includes" treating patients *with* such therapy, which does not infringe. *Grunenthal*, 919 F.3d at 1339. Because Defendants' labels "do not specifically encourage" using EPA without concurrent lipid altering therapy, there is "no induced infringement" as a matter of law.

920. In sum, Defendants are not liable for inducing infringement of claims 1 and 16 of the '728 patent, or claim 14 of the '715 patent, because Defendants' labels do not instruct physicians to treat patients without administering concurrent lipid altering therapy.

2. The seven asserted claims that allow co-administration with a statin were at least obvious to try regardless of the expected effects of EPA alone.

921. The remaining seven claims that do not exclude concurrent lipid altering therapy are all invalid as obvious—even under Plaintiffs' theory that skilled artisans lacked a reasonable expectation of success with EPA alone. This is because these seven claims allow adding a statin to EPA, and there is no dispute that this combination (which was actually used in the prior art) was reasonably expected to reduce triglycerides and Apo B without increasing LDL-C. The evidence of obviousness for these claims is clear and convincing. Indeed, it is fully supported by the testimony of Plaintiffs' own expert witness on validity, Dr. Toth.

922. As an initial matter, there is no dispute that "seven of the ten claims asserted in this case allow for use of a statin with icosapent." Toth Tr. 1886:11-14. This is because the seven claims that do not exclude concurrent lipid altering therapy contain the transitional phrase "comprising," which is "presumptively open ended" and "does not exclude additional, unrecited elements" from the scope of the claims—e.g., co-administering a statin. *Gillette Co. v. Energizer Holdings, Inc.*, 405

F.3d 1367, 1371-72 (Fed. Cir. 2005). Thus, if it was obvious to use purified EPA with a statin to achieve the claimed effects, the claims are invalid—regardless of whether the claimed effects were obvious to achieve with purified EPA alone. This is because "claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo*, 793 F.3d at 1281 (quotation omitted). In other words, if "the objective reach of the claim . . . . extends to what is obvious, it is invalid." *KSR*, 550 U.S. at 419.

923. There is also no dispute that, "by March 2008, it was known that EPA could be used with a statin." Toth Tr. 1876:25-1877:2. For example, "JELIS involved pure EPA with a statin." *Id*. at 1878:24-1879:1 (Toth). Nor is there any dispute that "pure EPA was given to at least one patient above 500 with a statin." *Id*. at 1878:16-23 (Toth). This was shown in Nakamura, in which all patients were administered "HMG-CoA-reductase inhibitors"—i.e., statins—and one patient had baseline triglycerides of approximately 560 mg/dL. FF ¶¶ 337, 340. Given that purified EPA was actually administered successfully with a statin to a patient with triglycerides above 500 mg/dL in the prior art, Plaintiffs cannot dispute that this combination was at least obvious to try. *See Nalpropion*, 934 F.3d at 1354-55 (rejecting patentee's argument that a skilled artisan would not have combined two drugs, where "[t]he inescapable, real-world fact here is that people of skill in the art *did combine*" the two drugs, which confirmed that "skilled artisans would have been motivated to combine the[m]").

924. Similarly, the Lovaza PDR (one of Defendants' key prior-art references) taught that Lovaza could be co-administered with simvastatin to patients with triglycerides above 500 mg/dL. FF ¶¶ 259-260, 330-331. As stated in the Lovaza PDR, Lovaza was indicated to treat "patients with very high (≥500 mg/dL) triglyceride levels," and "daily co-administration of simvastatin 80 mg with Lovaza 4 g did not" have any adverse drug-drug interactions. DX 1535 at 3. The Lovaza PDR also described a clinical study in which simvastatin was added to patients' daily regimen of 4 g Lovaza "to control their LDL-C." *Id*. at 2. Moreover, Plaintiffs admitted in their invalidity contentions that the "rise in LDL-C [with Lovaza] was often offset by concurrent treatment with statins," and "[t]he safety and efficacy of using prescription Omega-3 [fatty acids] in combination with a statin has been well-established." DX 1953 at 233. Thus, Defendants' combination of prior-art references, which

includes the Lovaza PDR, disclosed adding a statin to an omega-3 fatty acid to avoid increasing LDL-C.

925. There is also no dispute that a skilled artisan would understand that "statins can reduce LDL-C and apo B." Toth Tr. 1876:13-15. For example, Zocor (simvastatin), which was disclosed in the Lovaza PDR, was indicated to reduce both LDL-C and Apo B. DX 2005 at 1, 8. Lipitor (atorvastatin) was also indicated to reduce LDL-C and Apo B, and its label included clinical data showing that the drug reduced triglycerides and LDL-C in patients with triglycerides above 500 mg/dL. DX 3007 (2007 Lipitor label) at 11-12; DX 1986 (current Lipitor label) at 21.

926. Based on these undisputed facts, Dr. Toth agreed that a "skilled artisan, in 2008, would understand that if you give pure EPA with a statin," "you won't have as much of an LDL increase, or perhaps you won't increase LDL" at all. Toth Tr. 1879:16-20. Dr. Toth also agreed that "a skilled artisan, in March 2008, would understand that if you give pure EPA with a statin, you're likely to have an apo B decrease." *Id*. at 1879:21-25. Critically, Dr. Toth conceded that these results would be reasonably expected regardless of "whether the triglyceride level is 400 or 550." *Id*. at 1880:1-3. Dr. Toth thus agreed that it was "known in March 2008" that "pure EPA could be used with statins to reduce apo B and LDL-C." *Id*. at 1881:1-5. That obvious method of treatment falls within the scope of the seven claims that do not exclude concurrent lipid altering therapy. As Dr. Toth admitted, the "claims that allow for the use of a statin would include using 4 grams pure icosapent with a statin to . . . not have an LDL-C increase," as well as "to reduce apo B." *Id*. at 1886:15-24.

927. Based on Dr. Toth's admissions, there is not even a genuine dispute that the seven asserted claims that allow concurrent lipid altering therapy were at least obvious to try. Most importantly, Dr. Toth conceded that (a) purified EPA was co-administered with a statin in a patient with triglycerides of at least 500 mg/dL; and (b) a skilled artisan would have reasonably expected that combination to avoid increasing LDL-C and to reduce Apo B dL. *Id*. at 1878:16-23, 1879:16-1880:3. Thus, it was at least obvious to try administering purified EPA with a statin in a patient with triglycerides of at least 500 mg/dL, with a reasonable expectation that this combination would achieve all of the claimed effects—i.e., reduce triglycerides, avoid an increase in LDL-C, and reduce Apo B. Again, this is true *even accepting* Plaintiffs' argument that a skilled artisan would not reasonably

expect success in achieving those effects with purified EPA alone. Because it is undisputed that a skilled artisan would at least reasonably expect success with purified EPA *combined with a statin*, the seven asserted claims that allow that combination were at least obvious to try and thus invalid. *See In re Cuozzo*, 793 F.3d at 1281 ("claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter" (quotation omitted)).

928. For all the reasons discussed above in Part III.C.3., no secondary considerations suggest otherwise. In fact, two of Plaintiffs' asserted "unexpected results" are even weaker for these claims. It was clearly not "unexpected" that the combination of purified EPA and a statin would avoid increasing LDL-C or reduce Apo B. On the contrary, Dr. Toth admitted that a skilled artisan would have viewed both of those results as "likely." Toth Tr. 1879:16-1880:3.

929. Moreover, these seven claims do not just allow adding a statin; they also allow adding estriol. As discussed above, Plaintiffs criticized Kurabayashi, which showed a 6.9% reduction in Apo B, because patients in the study were taking estriol in addition to EPA. DX 1534 at 5. According to Plaintiffs, Kurabayashi only taught that EPA and estriol *together* reduced Apo B. Even if that were true, however, that combination falls within the scope of these seven claims. As a result, even if it were unexpected for EPA alone to reduce Apo B, that "showing of unexpected results" would be irrelevant because it is "not commensurate in scope with the degree of protection sought by the claimed subject matter," which allows the combination of EPA and estriol. *In re Harris*, 409 F.3d at 1344. Thus, the allegedly unexpected results of avoiding an increase in LDL-C and reducing Apo B do not support the seven claims that allow concurrent lipid altering therapy.

E. Defendants do not infringe the nine asserted claims that require specific lipid effects, and the remaining claim was at least obvious to try.

930. As a fourth, independent basis to grant judgment for Defendants, the nine asserted claims that require specific effects on a patient's lipids beyond a general reduction in triglycerides are not infringed, and the remaining asserted claim that does not require such effects—claim 1 of the '929 patent—is invalid because it was at least obvious to try.

1. Defendants' labels do not induce infringement of the nine claims that require minimum triglyceride reductions or controlling LDL-C or Apo B.

931. Nine of the 10 asserted claims require one or more of the following effects on a patient's lipids: (a) a reduction in triglycerides that is "statistically significant" or "of at least about" 10% or 20%;[18] (b) no increase, no "substantial[]" increase, no "statistically significant" increase, or no "more than 5%" increase in LDL-C levels;[19] or (c) a reduction in "apolipoprotein B."[20]

a. The labels do not instruct or specifically encourage doctors to use Defendants' products to achieve any of the claimed lipid effects.

932. There is no dispute, and the Court has already found, that Defendants' ANDA products are suitable for the substantial noninfringing use of treating a patient who has severe hypertriglyceridemia without achieving the claimed lipid effects. As the Court explained on summary judgment, "Defendants' potential ANDA drugs could be used in accordance with their proposed labels without achieving the specific effects required by those claims, and Plaintiffs' own clinical study explicitly establishes that some patients received the triglyceride reductions required by all Asserted Claims without getting the other health benefits required by the Other Health Benefits Claims—so at least some substantial non-infringing uses must exist." ECF No. 278 at 13 n.6. Indeed, Plaintiffs' MARINE study shows that at least 25% of patients will not experience each of the claimed effects. FF ¶¶ 128-131, 197, 213, 227. Thus, because Defendants' products have "substantial noninfringing uses, intent to induce infringement cannot be inferred." *Horizon*, 940 F.3d at 702. Instead, to prove inducement, Plaintiffs bear the burden of proving that the labeling actually "instructs"—i.e., "requires"—doctors to administer Defendants' products to achieve the claimed lipid effects. *Id*.

933. Critically, the Court's construction of the "effect terms" in these claims requires the patient to experience the effect *and* requires the prescribing physician to "intend" that the effect will occur—"in other words, the patent requires that the *intended* effect actually occur." ECF No. 135 at

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[18] '715 patent claim 14; '560 patent claims 4 and 17.

[19] '728 patent claim 1 and 16; '715 patent claim 14; '677 patent claim 1 and 8; '652 patent claim 1; '560 patent claim 4 and 17.

[20] '715 patent claim 14; '677 patent claim 8; '929 patent claim 5.

11 (emphasis added). Thus, for direct infringement, it is not enough that the claimed effect occurs. The doctor must prescribe the drug to the patient with the *intent* to achieve that effect. As a result, to induce infringement, Defendants' labels must contain an instruction that encourages doctors to administer Defendants' ANDA products with the intent to achieve the claimed lipid effects. Plaintiffs have not met their burden of proving that the labels contain any such instruction.

934. On their face, Defendants' labels contain no explicit or implicit instruction that encourages doctors to administer Defendants' products with the intent to achieve any of the claimed lipid effects. Defendants' products are indicated solely "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia," which does not specify any minimum reduction in triglycerides—or even mention LDL-C or Apo B. FF ¶¶ 192, 201, 217. As Dr. Budoff admitted, "defendants' products are not indicated specifically to reduce triglycerides by any particular amount," and are "not indicated to control LDL-C." Budoff Tr. 513:3-5, 519:23-25. As a result, "defendants' labels are not encouraging doctors to use the drug because it controls LDL-C." *Id*. at 513:14-16 (Budoff). The same is true for Apo B, which the "indication doesn't mention." Peck Tr. 1408:1-3. Dr. Budoff agreed, moreover, that "reducing apo B is not an intended result with regard to treating severe hypertriglyceridemia"—i.e., the indicated use for Defendants' products. Budoff Tr. 519:19-22. In fact, Plaintiffs previously sought a *separate* indication "to reduce . . . LDL-C [and] Apo B," which the FDA rejected. DX 1558 at 1. This distinguishes EPA from drugs such as Lipitor, which is expressly indicated "to reduce elevated total-C, LDL-C, apo B, and TG levels." DX 1986 at 3. Unlike that explicit instruction in the Lipitor label, nothing in either the Indications and Usage section or the Dosage and Administration section of Defendants' labels even suggests the use of Defendants' products to achieve the claimed lipid effects. FF ¶¶ 192-196, 201-210, 217-226.

935. As Dr. Budoff conceded, Plaintiffs' infringement theory for the claimed lipid effects thus requires drawing an "inference [that] goes beyond the scope of the indication." Budoff Tr. 512:3-5. But again, given the substantial noninfringing uses of Defendants' products, inducement "cannot be inferred." *Horizon*, 940 F.3d at 701. Even assuming that the indication "includes" using the

products for the claimed lipid effects, it "do[es] not specifically encourage [that] use," so there is "no induced infringement." *Grunenthal*, 919 F.3d at 1339.

936. In arguing otherwise, Plaintiffs rely exclusively on the Clinical Studies section, which is the only section that even mentions the claimed lipid effects. Specifically, that section includes a table with the median lipid effects reported in the 12-week MARINE trial, and includes the following statement below the table: "Icosapent ethyl 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." FF ¶¶ 194-195, 204-205, 221-222.

937. There is no legal basis, however, to infer an implied use from the Clinical Studies section. FDA regulations make clear that the Clinical Studies section "must not imply or suggest indications or uses . . . not stated in the 'Indications and Usage' or 'Dosage and Administration' section." 21 C.F.R. § 201.57(c)(15)(i). As discussed above, the only case that Plaintiffs have cited in which the Federal Circuit relied on the Clinical Studies section, *Sanofi*, involved a label in which the Indications and Usage section "expressly direct[ed]" doctors to the Clinical Studies section "for elaboration of" the indicated use. *Sanofi II*, 875 F.3d at 645. Again, there is no such "express direct[ion] here." The Indications and Usage section does not even mention the Clinical Studies section.

938. Even if it were proper to consider the Clinical Studies section to evaluate other uses of EPA, neither the table nor the statement below the table instructs doctors to infringe. As to the table, it merely reports median data on the effects of Vascepa in 76 individuals. DX 2256 (Hikma Label) at 7-8; DX 2266 (DRL Label) at 9. The table does not instruct doctors to do anything, let alone use Defendants' products to achieve the claimed effects. At most, the table describes the fact that the claimed effects occurred in some patients. "Merely describing the infringing use . . . will not suffice," however—"specific intent and action to induce infringement must be proven." *Horizon*, 940 F.3d at 702. Even assuming that the reported median data "describe the infringing mode," that "is not the same as recommending, encouraging, or promoting an infringing use, or suggesting that

an infringing use 'should' be performed." *Takeda*, 785 F.3d at 631 (citations, quotation marks, and alterations omitted).

939. Moreover, the data in the table do not describe whether the claimed effects will occur in any given patient. As Dr. Budoff admitted, "median data from a clinical trial may or may not relate to an individual patient." Budoff Tr. 512:6-9. If anything, a doctor would understand from the data that Defendants' products could *increase* LDL-C. The reported confidence interval for LDL-C includes an increase of "+8" percent, which Dr. Budoff admitted was "a clinically meaningful increase." FF ¶¶ 207-208; DX 2256 (Hikma Label) at 7-8); DX 2266 (DRL Label) at 9; Budoff Tr. 514:20-22. Based on that result, Dr. Budoff conceded that a "doctor would understand that some patients taking icosapent will actually experience a clinically significant LDL-C increase." Budoff Tr. 515:3-8. That is a far cry from an instruction that specifically encourages doctors to administer EPA to avoid increasing LDL-C.

940. While the median data show a reduction in Apo B (by just 4%, or 9% relative to placebo), there is no evidence that this reduction is clinically significant—or that it even encourages doctors to measure Apo B levels, let alone prescribe EPA to reduce those levels. Indeed, Dr. Budoff admitted that he "do[es]n't send patients to the lab for apo B measurements routinely," and only reviews the data "[i]f it's available." Budoff Tr. 519:16-18. Dr. Sheinberg does not use Vascepa to reduce Apo B either. Sheinberg Tr. 643:16-21. As he emphasized, the reported, single-digit reduction in Apo B "is absolutely not clinically significant," and "us[ing] this medication specifically for apo B reduction" would be "a breach of the standard of care." *Id*. at 643:16-25.

941. As for the statement below the table, it adds nothing to the reported median data, much less a relevant instruction. Dr. Budoff admitted that the statement is simply "reporting on observations concerning the clinical trial that's being reported in [the] table." Budoff Tr. 511:9-12. As he conceded, "these are not instructions on how to use icosapent." *Id.* at 511:13-15.

942. Dr. Budoff's only material opinion about this statement is that "doctors will compare" it "to the Lovaza warning about LDL-C," and that based on this comparison, doctors will be encouraged to treat their patients with EPA instead of Lovaza because of its more favorable effects on LDL-C. Budoff Tr. 515:17-20. But there is no legal basis for that theory, which impermissibly

"asks [the Court] to look outside the label to understand the alleged implicit encouragement in the label." *Takeda*, 785 F.3d at 634. Under a proper inducement theory, a doctor "d[oes] not have to consult anything outside of the label to infringe." *Id.* Dr. Budoff's theory that a doctor would compare Defendants' labels to the Lovaza label contravenes that principle, and would make the inducement inquiry turn on Defendants' "mere knowledge" of the Lovaza labelling (which Defendants do not control) instead of the required "active steps taken to encourage direct infringement" with instructions in their own labelling. *Id*. (quotation omitted).

943. Nothing in Defendants' labels instructs doctors to perform the comparison between the Clinical Studies section and the Lovaza label that Dr. Budoff's theory requires. Dr. Budoff admitted that "Defendants' labels never tell doctors to compare the icosapent clinical trial to the Lovaza clinical trial," or even "refer to the Lovaza label at all." Budoff Tr. 516:22-517:2. If anything, the labels instruct doctors *not* to make that comparison. In the Adverse Reactions section, the labels warn that "[b]ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice." DX 2256 (Hikma Label) at 3; DX 2266 (DRL Label) at 3. Dr. Budoff agreed that this "tell[s] doctors and warn[s] them against comparing adverse reactions from two clinical trials involving 2 different drugs." Budoff Tr. 517:16-19. He further agreed that a "doctor reading defendants' labels would understand that two clinical trials involving two different drugs are conducted under different situations, and they may or may not be comparable." *Id.* at 518:3-7. Thus, the labels actually warn doctors *not* to compare the reported clinical studies for Vascepa and Lovaza. Sheinberg Tr. 644:5-14. At a minimum, the labels do not encourage that comparison.

944. Without that comparison, however, Dr. Budoff's theory that the Clinical Studies section encourages doctors to use Defendants' products to avoid increasing LDL-C falls apart. Indeed, Dr. Budoff admitted that the "LDL-C statement in [the] label would carry significance to a doctor *only because and if* the doctor understood that Lovaza had this side effect." Budoff Tr. 516:15-21 (emphasis added). Without that understanding from the Lovaza label, Dr. Budoff conceded that "it wouldn't mean much to the doctor to say there was no LDL-C increase." *Id.* at 516:19-21. As a

result, there is no evidence supporting Dr. Budoff's theory that the labelling encourages doctors to prescribe Defendants' products to avoid an increase in LDL-C.

945. In sum, Plaintiffs failed to prove that Defendants' labels instruct doctors to administer Defendants' products to achieve the claimed lipid effects—i.e., a minimum reduction in triglycerides, no increase in LDL-C, or a reduction in Apo B. Neither the Indications and Usage section nor the Dosage and Administration section even mentions these claimed effects, which appear only in the Clinical Studies section. It is undisputed that the Clinical Studies section does not set forth any instruction, let alone an instruction to use EPA to achieve the claimed effects. Moreover, Dr. Budoff's only theory for why a doctor would be encouraged to use EPA to avoid an LDL-C increase—namely, that the doctor would compare the Clinical Studies sections of Defendants' labels and the Lovaza label—is both legally flawed and unsupported by the labels themselves. Thus, there is no basis to conclude that Defendants will induce infringement of the nine asserted claims that require specific effects on a patient's lipids beyond a general reduction in triglycerides.

b. The claimed lipid effects to avoid an increase in LDL-C and reduce Apo B levels are not approved uses of EPA.

946. Independently, Defendants' labels cannot induce infringement of the asserted claims that require controlling LDL-C[21] or Apo B[22] because those uses of Defendants' products are not even approved by the FDA. The Federal Circuit has repeatedly held that "a method of use patent holder may not sue an ANDA applicant for induced infringement of its patent, if the ANDA applicant is not seeking FDA approval for the use claimed in the patent and if the use claimed in the patent is not FDA-approved." *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1332 (Fed. Cir. 2003); *accord Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1326 (Fed. Cir. 2012); *AstraZeneca Pharms. LP v. Apotex Corp.*, 669 F.3d 1370, 1379 (Fed. Cir. 2012) ("[A] patented method of using a drug can only be infringed under § 271(e)(2) by filing an ANDA that seeks approval to market the drug for that use."); *Warner-Lambert*, 316 F.3d at 1354-55 ("[I]t is not an act of infringement to

[21] '728 patent claim 1 and 16; '715 patent claim 14; '677 patent claim 1 and 8; '652 patent claim 1; '560 patent claim 4 and 17.

[22] '715 patent claim 14; '677 patent claim 8; '929 patent claim 5.

submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA.").

947. As made clear in *Bayer*, a patent holder's inability to sue ANDA applicants for unapproved uses includes potential uses described in the drug labeling. In *Bayer*, the method-of-use patent claimed to achieve three effects: a contraceptive effect, an anti-androgenic (anti-acne) effect, and an anti-aldosterone effect (reducing water retention). 676 F.3d at 1319-1320. Bayer's drug, however, was only approved for oral contraception. *Id*. The Federal Circuit rejected Bayer's arguments that the generic defendants' labels encouraged the unapproved uses, even though the anti-androgenic and anti-aldosterone effects were presented in the Clinical Pharmacology and Pharmacodynamics sections of the drug label. *Id*. at 1322, 1325-26. As the Federal Circuit explained, "the fact that certain of the effects of a drug are described in the Clinical Pharmacology section of the label does not mean that the FDA has approved the use of the drug to produce those effects; it only ensures that physicians are aware of the full range of the drug's pharmacological effects." *Id.* at 1323.

948. The logic behind *Bayer* and its progeny is straightforward. Because the Patent Act limits liability under § 271(b) to one who "actively induces infringement," it requires an element of scienter: "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." *Warner-Lambert*, 316 F.3d at 1364. In a Hatch-Waxman case, these inquiries are "limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed." *Id*. It follows that "the request to make and sell a drug labeled with a permissible (non-infringing) use cannot reasonably be interpreted as an act of infringement (induced or otherwise) with respect to a patent on an unapproved use, as the ANDA does not induce anyone to perform the unapproved acts required to infringe." *Id*. at 1364-65.

949. That principle bars a finding of infringement for claims that require administering EPA to reduce or not increase a patient's LDL-C or Apo B levels. The FDA approved no such use of EPA. It is "[t]he FDA-approved label for an approved drug [that] indicates whether the FDA has approved a particular method of use for that drug." *Bayer*, 676 F.3d at 1322. Here, the FDA-approved labelling indicates that the FDA has approved EPA only to reduce triglycerides by some unspecified

degree, without regard to LDL-C or Apo B. FF ¶¶ 192, 201, 217. Those parameters are not even mentioned in the approved indication, or anywhere else in the "Indications and Usage" section of the label that must set forth the uses of the drug that the FDA has approved. 21 C.F.R. § 201.57(a)(6), (c)(2). In fact, the FDA *rejected* an indication that Plaintiffs sought for controlling LDL-C and Apo B. DX 1558 at 1 (rejecting proposed indication that included "reduc[ing] . . . Apo B, LDL-C").

950. Plaintiffs cannot rely on the median results reported in the Clinical Studies section to show otherwise. "[W]hether other effects may be described outside the Indications and Usage section of the FDA-approved label does not address the issue" of induced infringement. *Bayer*, 676 F.3d at 1323. Under FDA regulations, only the "Indications and Usage section of the label" may set forth an indication; "indications or uses 'must not be implied or suggested in other sections of the labeling if not included in this section.'" *Id.* at 1322-23 (quoting 21 C.F.R. § 201.57(c)(2)(iv)). Thus, "[t]he fact that certain of the effects of a drug are described in [other sections of] the . . . label does not mean that the FDA has approved the use of the drug to produce those effects." *Id.* at 1323.

951. Likewise, it is immaterial whether other parts of the labelling describe "the drug's pharmacological effects . . . when prescribing the drug for a purpose set forth in the Indications and Usage section." *Id*. As the Federal Circuit made clear in *Bayer*, there is no inducement if the FDA has not approved the drug to produce the claimed effect, even if the drug "necessarily" produces that effect when taken as directed. *Id.* at 1321 (citing *Allergan*, 324 F.3d at 1324—"because those [claimed] uses were not approved by the FDA, the generic drug applicant could not be liable for infringement under section 271(e)(2)(A), even though [the drug] necessarily had those [claimed] effects in patients who took the drug for the approved purpose").

952. It follows that any reference in the Clinical Studies section to effects on LDL-C and Apo B "is certainly not a direct indication of an appropriate use for [EPA], and even if it could be considered an 'implied or suggested' indication of an appropriate use, the [FDA] regulation expressly states that such implied or suggested uses do not constitute approved uses." *Id.* at 1323. Nor can Plaintiffs rely on expert "opinion [that] is contrary to the contents of the FDA-approved label." *Id.* at 1325. Because Defendants "have submitted ANDAs seeking approval to market [EPA] for uses

that are not subject to [Plaintiffs'] method of use patents, [Plaintiffs] do[] not state a claim for infringement" by inducement of these claims. *AstraZeneca*, 669 F.3d at 1380.

2. The single claim that does not exclude an LDL-C increase or require an Apo B reduction was at least obvious to try.

953. The sole remaining asserted claim—claim 1 of the '929 patent—does not require any specific lipid effects, and does not exclude the use of other lipid-altering drugs such as statins and estriol. Given the breadth of this claim, clear and convincing evidence proves that it was at least obvious to try, for all the reasons set forth above in Parts III.C.1.b.i. and III.C.1.b.ii.

954. Importantly, because this claim does not exclude an increase in LDL-C, and does not require a reduction in Apo B, it was at least obvious to try regardless of whether those results were reasonably expected as of the priority date. As the Federal Circuit has repeatedly made clear, "the person of ordinary skill need only have a reasonable expectation of success of developing the *claimed* invention." *Allergan*, 726 F.3d at 1292 (emphasis added); *see also Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) ("The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet *the limitations of the claimed invention*"—the "correct inquiry" is whether there is "a reasonable expectation of achieving *what is claimed* in the patent-at-issue" (emphasis added)).

955. In claim 1 of the '929 patent, the "claimed invention" only requires "reducing triglycerides"—without regard to whether that reduction is accompanied by effects on LDL-C and Apo B. There is no dispute that a skilled artisan would have reasonably expected the general reduction in triglycerides required by this claim. Dr. Toth admitted that "based on the prior art, a skilled artisan, as of March 2008, would have reasonably expected purified EPA to reduce triglyceride levels above 500." Toth Tr. 1860:12-15. Thus, it is undisputed that a skilled artisan would have had a reasonable expectation of success in practicing claim 1 of the '929 patent. Heinecke Tr. 763:14-764:15. This is true even if the Court were to accept Plaintiffs' arguments that a skilled artisan would not have reasonably expected the LDL-C or Apo B effects required by the other nine asserted claims (which, as discussed in the previous section, are not infringed).

956. No secondary considerations weigh against this conclusion. In addition to the reasons set forth in Part III.C.3., which apply equally to claim 1 of the '929 patent, the alleged secondary considerations regarding LDL-C and Apo B are not commensurate in scope with this claim. As confirmed by Plaintiffs' MARINE study, there is no dispute that at least 25% of patients do not experience the alleged benefits of avoiding an increase in LDL-C or reducing Apo B. FF ¶¶ 130-131, 213, 227; ECF No. 278 at 13 n.6. For those patients, LDL-C and Apo B levels actually *increased*. *Id*. Claim 1 of the '929 patent broadly covers the treatment of those patients, for whom the alleged benefits of Vascepa do not apply. Because the alleged LDL-C and Apo B benefits are "not commensurate with the full scope of" the claim, they fail to support nonobviousness as "lacking a nexus with the scope of the . . . claimed invention." *Allergan*, 754 F.3d at 965; Heinecke Tr. 807:25-808:12, 814:18-25.

957. Accordingly, Defendants do not infringe the nine asserted claims that require specific lipid effects, and the single claim that does not require such effects is invalid.

F. Alternatively, all asserted claims are invalid for lack of written description.

958. Defendants recognize that the Court entered partial summary judgment for Plaintiffs on Defendants' written-description defense under 35 U.S.C. § 112, ¶ 1. ECF No. 278 at 19. For purposes of appellate preservation, however, Defendants contend that to the extent the Court accepts Plaintiffs' arguments that any asserted claim would not have been obvious because there was no reasonable expectation of success based on the prior art, any such claim lacks an adequate written description because a skilled artisan would not have believed, based on the patents' specification, that the named inventors had possession of the claimed invention as of the filing date. Simply put, the specification adds nothing to the teachings of the prior art that would indicate to a skilled artisan that the named inventors discovered anything that was not already known. Defendants fully incorporate by reference their opposition to Plaintiffs' partial summary judgment motion, ECF No. 247, which sets forth the basis for Defendants' alternative, written-description defense.

959. As Defendants explained, the Federal Circuit invalidated claims for lacking written description under analogous circumstances in *Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368 (Fed. Cir. 2019). There, as here, "[t]he Generics

defended against the [patentee's] infringement assertions by alleging that the asserted patents are invalid as obvious." *Id*. at 1374. After trial, the district court ruled for the patentee, accepting the patentee's argument "that none of the asserted claims are obvious over the prior art because" a skilled artisan "would not have reasonably expected [the claimed method] to work." *Id*. at 1374-75. But the defendants had an alternative defense: They "argued that, if they lose on their obviousness contention, then the claims lack written description support . . . because ordinarily skilled artisans would not have expected [the invention] to work and the specification provides no experimental data or analytical reasoning showing the inventor possessed" it. *Id*. at 1375. The Federal Circuit agreed, calling the defendants' argument "straightforward" in light of "the district court [having] found upon [the patentee]'s insistence as part of its obviousness analysis that ordinarily skilled artisans would not have expected [the drug] to be effective" for its claimed purpose. *Id*. at 1377. The Federal Circuit held: "In light of the fact that the specification provides nothing more than the mere claim that [the invention] might work, even though persons of ordinary skill in the art would not have thought it would work, the specification is fatally flawed." *Id*. at 1381. Thus, based on the patentee's insistence at trial that a skilled artisan "would not have known or understood that [the claimed drug] is effective," "there [wa]s nothing in the specification of the patents-in-suit showing that the inventor *actually invented* the invention claimed," as required by section 112. *Id*. at 1380 (quotation omitted).

960. *Nuvo* applies here. If the Court were to "f[i]nd upon [Plaintiffs]' insistence as part of its obviousness analysis that ordinarily skilled artisans would not have expected [EPA] to be effective" for achieving the claimed effects based on the prior art, the asserted claims would be invalid as not described because "the specification provides no experimental data or analytical reasoning showing the inventor possessed" a method to achieve those effects. *Id*. at 1375, 1377.

961. Defendants respectfully submit that this defense was not waived. Defendants contended that the asserted claims are invalid for failure to comply with 35 U.S.C. § 112 in their counterclaims, and more specifically contended that the asserted claims are invalid for lack of written description in their invalidity contentions under the Court's Local Patent Rules 1-8 and 1-9. There was no need for Defendants to present their own expert testimony to preserve this defense, because it is an alternative defense based on *Plaintiffs'* expert testimony regarding the state of the prior art.

Regardless, there is no legal requirement for expert testimony on the ultimate issue of written description. *See, e.g.*, *Univ. Of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004) ("[A] patent can be held invalid for failure to meet the written description requirement, based solely on the language of the patent specification. After all, it is in the patent specification where the written description requirement must be met."); *Adang v. Umbeck*, 2007 WL 3120323, at *2 (Fed. Cir. Oct. 25, 2007) (rejecting the "argu[ment] that [a patent challenger] failed to present any expert testimony" on written description; holding that "there is no strict requirement for extrinsic evidence (expert or otherwise) . . . [to] determine whether the written description requirement has been satisfied").

IV. CONCLUSION

962. For the reasons set forth above, Defendants are entitled to judgment in their favor on four independent grounds:

- First, Defendants are not liable for inducing infringement of any asserted claim because the labels for their proposed generic products do not instruct physicians to administer Defendants' products for at least 12 weeks. Thus, judgment of noninfringement should be entered as to all asserted claims.[23]
- Second, all asserted claims are invalid under 35 U.S.C. § 103 because they were obvious, or at least obvious to try, in view of the prior art as of the priority date. Thus, judgment of invalidity should be entered as to all asserted claims.[24]
- Third, Defendants will not induce infringement of the three asserted claims that exclude concurrent lipid altering therapy, and the remaining seven claims that allow such therapy were at least obvious to try because co-administering a statin was reasonably expected to achieve all of the claimed effects. Thus, judgment of noninfringement should be entered as to three asserted claims,[25] and judgment of invalidity should be entered as to seven asserted claims.[26]
- Fourth, Defendants will not induce infringement of the nine asserted claims that require specific effects on patients' lipids, and the remaining claim—which requires no lipid effects other than reducing triglycerides—was at least obvious to try. Thus,

[23] Claims 1 and 16 of the '728 patent, claim 14 of the '715 patent, claims 1 and 8 of the '677 patent, claim 1 of the '652 patent, claims 4 and 17 of the '560 patent, and claims 1 and 5 of the '929 patent.

[24] *Id*.

[25] Claims 1 and 16 of the '728 patent, and claim 14 of the '715 patent.

[26] Claims 1 and 8 of the '677 patent, claim 1 of the '652 patent, claims 4 and 17 of the '560 patent, and claims 1 and 5 of the '929 patent.

judgment of noninfringement should be entered as to nine asserted claims,[27] and judgment of invalidity should be entered as to one asserted claim.[28]

963. Defendants are thus entitled to judgment as to all of Plaintiffs' claims for infringement, and as to all of Defendants' counterclaims for noninfringement and invalidity.

[27] Claims 1 and 16 of the '728 patent, claim 14 of the '715 patent, claims 1 and 8 of the '677 patent, claim 1 of the '652 patent, claims 4 and 17 of the '560 patent, and claim 5 of the '929 patent.

[28] Claim 1 of the '929 patent.

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CERTIFICATE OF SERVICE

Pursuant to FRCP 5(b) and Section IV of the District of Nevada Electronic Filing Procedures, I hereby certify that I am an employee of WINSTON & STRAWN, LLP, and on this 14th day of February, 2020, I served the document entitled, **DEFENDANTS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW**, on counsel of record through the CM/ECF system.

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